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(54) **SELECTIVE REMOVAL OF AGE-MODIFIED CELLS FOR TREATMENT OF ATHEROSCLEROSIS**

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(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,217,344	A	8/1980	Vanlerberghe et al.
4,900,747	A	2/1990	Vlassara et al.
4,911,928	A	3/1990	Wallach
4,917,951	A	4/1990	Wallach
5,494,791	A	2/1996	Cohen
5,518,720	A	5/1996	Cohen
5,601,526	A	2/1997	Chapelon et al.
5,620,479	A	4/1997	Diederich
5,664,570	A	9/1997	Bishop
5,693,762	A	12/1997	Queen et al.
5,702,704	A	12/1997	Bucala
5,766,590	A	6/1998	Founds et al.
5,811,075	A	9/1998	Vlassara et al.
5,817,771	A	10/1998	Bayley et al.
5,984,882	A	11/1999	Rosenschein et al.
6,067,859	A	5/2000	Kas et al.
6,090,382	A	7/2000	Salfeld et al.
6,176,842	B1	1/2001	Tachibana et al.
6,245,318	B1	6/2001	Klibanov et al.
6,309,355	B1	10/2001	Cain et al.
6,380,165	B1	4/2002	Al-Abed et al.
6,387,373	B1	5/2002	Wright et al.
6,670,136	B2	12/2003	Schmidt et al.
6,676,963	B1	1/2004	Lanza et al.
6,818,215	B2	11/2004	Smith et al.
6,821,274	B2	11/2004	McHale et al.
7,033,574	B1	4/2006	Schneider et al.
7,101,838	B2	9/2006	Stern et al.
7,256,273	B2	8/2007	Basi et al.
7,347,855	B2	3/2008	Eshel et al.
7,358,226	B2	4/2008	Dayton et al.
7,367,988	B1	5/2008	Litovitz
7,751,057	B2	7/2010	Oldenburg et al.
7,815,570	B2	10/2010	Eshel et al.
8,323,651	B2	12/2012	Gu et al.
8,343,420	B2	1/2013	Cioanta et al.
8,398,977	B2	3/2013	Bleck et al.
8,721,571	B2	5/2014	Gruber
9,161,810	B2	10/2015	Gruber
9,320,919	B2	4/2016	Gruber
9,649,376	B2	5/2017	Gruber
9,993,535	B2	6/2018	Gruber
2002/0193784	A1	12/2002	McHale et al.
2003/0073138	A1	4/2003	Kientsch-Engel et al.
2003/0170173	A1	9/2003	Klaveness et al.
2003/0229283	A1	12/2003	Craig et al.
2004/0039416	A1	2/2004	Myhr
2004/0141922	A1	7/2004	Klaveness et al.
2004/0208826	A1	10/2004	Schneider et al.
2004/0229830	A1	11/2004	Tachibana et al.

(Continued)

FOREIGN PATENT DOCUMENTS

AU	2009248945	11/2012
AU	2009248945	4/2013

(Continued)

OTHER PUBLICATIONS

International Search Report and Written Opinion dated Sep. 29, 2017 for PCT application No. PCT/US2017/027773.

Capparelli, C. et al., "Autophagy and senescence in cancer-associated fibroblasts metabolically supports tumor growth and metastasis via glycolysis and ketone production", Cell Cycle, vol. 11, No. 12, pp. 2285-2302, (2012).

""Shelf life" of blood? Shorter than we think", Johns Hopkins Medicine, pp. 1-2 found at www.hopkinsmedicine.org/news/media/releases/shelf_life_of_blood_shorter_than_we_think, (2013).

(Continued)

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(57) **ABSTRACT**

A method of treating atherosclerosis comprises removing AGE-modified cells from a patient. The AGE-modified cells include erythrocytes, intima cells, endothelial cells, smooth muscle cells, macrophages, and foam cells. A variety of techniques, such as ultrasound and binding with an anti-AGE antibody, may be used to identify and remove the AGE-modified cells.

28 Claims, No Drawings

(56) **References Cited**

U.S. PATENT DOCUMENTS

2005/0084538	A1	4/2005	Dayton et al.
2005/0283098	A1	12/2005	Conston et al.
2006/0078501	A1	4/2006	Goertz et al.
2006/0122543	A1	6/2006	Mayer et al.
2006/0188883	A1	8/2006	Murray et al.
2007/0059247	A1	3/2007	Lindner et al.
2007/0065415	A1	3/2007	Kleinsek et al.
2007/0065443	A1	3/2007	Tobia
2007/0083120	A1	4/2007	Cain et al.
2007/0128117	A1	6/2007	Bettinger et al.
2007/0129633	A1	6/2007	Lee et al.
2008/0019986	A1	1/2008	Stern et al.
2008/0051680	A1	2/2008	Luebcke
2008/0063603	A1	3/2008	Schneider et al.
2008/0139942	A1	6/2008	Gaud et al.
2008/0160506	A1	7/2008	Liu et al.
2009/0076390	A1	3/2009	Lee et al.
2009/0306552	A1	12/2009	Furuzono et al.
2010/0028359	A1	2/2010	Gu et al.
2010/0226932	A1	9/2010	Smith et al.
2011/0105961	A1	5/2011	Gruber
2011/0319499	A1	12/2011	Semba et al.
2012/0130287	A1	5/2012	Gruber
2012/0183534	A1	7/2012	Gruber
2013/0131006	A1	5/2013	Hee et al.
2013/0243785	A1	9/2013	Gruber
2014/0303526	A1	10/2014	Gruber
2016/0101299	A1	4/2016	Gruber
2016/0152697	A1	6/2016	Gruber
2016/0175413	A1	6/2016	Gruber
2016/0215043	A1	7/2016	Gruber
2016/0339019	A1	11/2016	Laberge et al.
2017/0247472	A1	8/2017	Gruber
2018/0044411	A1	2/2018	Gruber
2018/0111982	A2	4/2018	Gruber

FOREIGN PATENT DOCUMENTS

AU	2009248945	2/2014
AU	2009/248945	5/2014
AU	2011332143	6/2015
AU	2014202548	6/2015
AU	2011332143	1/2016
AU	2014202548	1/2016
AU	2014202548	4/2016
AU	2014202548	6/2016
AU	2016204196	8/2016
CA	2724886	6/2014
CA	2724886	2/2015
CA	2724886	9/2015
CA	2724886	4/2016
CA	2818647	10/2016
CA	2724886	2/2017
CA	2818647	4/2017
CA	2724886	5/2017
CN	200980118817.6	5/2012
CN	200980118817.6	2/2013
CN	200980118817.6	10/2013
CN	200980118817.6	5/2014
CN	200980118817.6	10/2014
CN	200980118817.6	3/2015
CN	201510303227.8	6/2016
CN	201510303227.8	12/2016
CN	201510303227.8	5/2017
DE	102008009461	8/2009
EP	0 259 893	3/1988
EP	1 415 997	5/2004
EP	09 751 639.7	11/2011
EP	09 751 639.7	6/2012
EP	09 751 639.7	1/2013
EP	09751639.7	7/2013
EP	09751639.7	1/2014
EP	14170802.4	9/2014
EP	14170802.4	7/2015
EP	14170802.4	12/2015
EP	14170802.4	11/2016
EP	16198527.0	2/2017
EP	11776932.3	3/2017
EP	11776932.3	8/2017
IL	209513	8/2012
IL	209513	5/2013
IL	209513	5/2014
IL	209513	12/2014
IL	240242	4/2016
IL	240242	1/2017
IL	248652	5/2017
IN	4875/KOLNP/2010	12/2016
JP	2003/160599	6/2003
JP	2006-249015	9/2006
JP	2011-511734	11/2013
JP	2011-511734	12/2014
JP	2015-076575	6/2015
JP	2015-076575	1/2016
JP	2016-098558	7/2016
JP	2016-098558	12/2016
KR	10-2012-7026063	7/2012
KR	10-2010-7026063	2/2013
KR	10-2010-7026063	9/2013
KR	10-2010-7026063	12/2013
KR	10-2013-7028228	6/2014
KR	10-2010-7026063	7/2014
KR	10-2012-7026483	7/2014
KR	10-2012-7026483	2/2015
KR	10-2013-7028228	4/2015
KR	10-2015-7007520	4/2015
KR	10-2015-7007520	11/2015
MX	2010/012473	7/2013
MX	2010/012473	3/2014
MX	2010/012473	6/2014
MX	MX/a/2013/013310	7/2015
MX	MX/a/2013/013310	4/2016
MX	MX/a/2013/013310	2/2017
RU	2010152693	12/2012
RU	20100152693	4/2013
RU	2010152693	5/2014
RU	2010152693	12/2014
RU	2015114990	7/2016
RU	2015114990	1/2017
RU	2017113349	5/2017
RU	2015114990	8/2017
WO	1996/20958	7/1996
WO	1997/49429	12/1997
WO	1999/07893	2/1999
WO	1999/14587	3/1999
WO	1999/64463	12/1999
WO	2000/20458	4/2000
WO	2004/011460	2/2004
WO	2004/016229	2/2004
WO	2004/076677	9/2004
WO	2006/012415	2/2006
WO	2006/017647	2/2006
WO	2006/040597	4/2006
WO	PCT/US2009/44951	7/2009
WO	2009/136382	11/2009
WO	2009/143411	11/2009
WO	2010/005531	1/2010
WO	PCT/US2009/44951	12/2010
WO	2012/047629	4/2012
WO	PCT/US2011/053399	4/2012
WO	2012/071269	5/2012
WO	PCT/US12/31446	6/2012
WO	PCT/US2011/061387	6/2012
WO	2012/135616	10/2012
WO	2013/009785	1/2013
WO	2013/043161	3/2013
WO	11776932.3	4/2013
WO	2013/070468	5/2013
WO	PCT/US2011/061387	5/2013
WO	PCT/US2012/031446	10/2013
WO	2015/112835	7/2015
WO	2015/116740	8/2015
WO	2016/044252	3/2016
WO	PCT/US2015/050154	3/2016
WO	PCT/US2016/034880	8/2016

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO	PCT/US2016/039076	12/2016
WO	PCT/US2015/050154	3/2017
WO	2017/065837	4/2017
WO	PCT/US2017/018185	5/2017
WO	2017/181116	10/2017

OTHER PUBLICATIONS

Garay-Sevilla, M.E. et al., "Advanced glycosylation end products in skin, serum, saliva and urine and its association with complications of patients with Type 2 diabetes mellitus", Journal of Endocrinological Investigation, vol. 28, No. 5, pp. 223-230, (2005).

Joyal, S.V., "Aging and Glycation", Life Extension Magazine, issue 4, pp. 1-7, found at www.lifeextension.com/Magazine/2008/4/Aging-And-Glycation/Page-01, (2008).

Egberts, J-H. et al., "Anti-tumor necrosis factor therapy inhibits pancreatic tumor growth and metastasis", Cancer Research, vol. 68, pp. 1443-1450, (2008).

Lowe, R. et al., "Buccals are likely to be a more informative surrogate tissue than blood for epigenome-wide association studies", Epigenetics, vol. 8, No. 4, pp. 445-454, (2013).

Bian, C. et al., "Clinical outcome and expression of mutant P53, P16, and Smad4 in lung adenocarcinoma: a prospective study", World Journal of Surgical Oncology, vol. 13, No. 128, pp. 1-8, (2015).

Tape, C.J. et al., "Oncogenic KRAS regulates tumor cell signaling via stromal reciprocation", Cell, vol. 165, pp. 910-920, (2016).

Product description for "CD8+CD57+ T Cell Isolation Kit, human", Miltenyi Biotec, pp. 1-4, found at www.miltenyibiotec.com/en/products-and-services/macs-cell-separation/cell-separation-reagents/t-cells/cd8-cd57-t-cell-isolation-kit-human.aspx, printed on Aug. 16, 2017.

Warrington, K.J. et al., "CD28 loss in senescent $CD4^+$ T cells: reversal by interleukin-12 stimulation", Blood, vol. 101, No. 9, pp. 3543-3549, (2003).

Kared, H. et al., "CD57 in human natural killer cells and T-lymphocytes", Cancer Immunology, Immunotherapy, vol. 65, issue 4, pp. 441-452, (2016).

Li, Z. et al., "Cdkn2a suppresses metastasis in squamous cell carcinomas induced by the gain-of-function mutant $p53^{R172H}$", The Journal of Pathology, vol. 240, issue 2, pp. 224-234, (2016). (Abstract Only).

Demaria, M. et al., "Cellular senescence promotes adverse effects of chemotherapy and cancer relapse", Cancer Discovery, vol. 7, pp. 165-176, (2017).

Niu, L. et al., "Free and protein-bound N^{ϵ}-carboxymethyllysine and N^{ϵ}-carboxyethyllysine in fish muscle: Biological variation and effects of heat treatment", Journal of Food Composition and Analysis, vol. 57, pp. 56-63, (2017).

Yoon, M-S. et al., "Characterisation of advanced glycation endproducts in saliva from patients with diabetes mellitus", Biochemical and Biophysical Research Communications, vol. 323, issue 2, pp. 377-381, (2004).

Product description for "Carboxymethyl Lysine (CML) ELISA", Kamiya Biomedical Company, pp. 1-7, found at www.k-assay.com/pdf/Kt-32428.pdf, printed on Aug. 16, 2017.

Baar, M.P. et al., "Targeted apoptosis of senescent cells restores tissue homeostasis in response to chemotoxicity and aging", Cell, vol. 169, pp. 132-147, (2017).

Kim, Y.H. et al., "Senescent tumor cells lead the collective invasion in thyroid cancer", Nature Communications, pp. 1-14, (2017).

Ciccone, T.G. et al., "Reversing OA-new treatment on the horizon", Practical Pain Management, pp. 1-5, found at www.practicalpainmanagement.com/resources/news-and-research/reversing-oa-new-treatment-horizon, printed on Aug. 17, 2017.

Cook, L.S., "Learning about blood component therapy", Nursing, vol. 39, No. 4, pp. 30-33, (2009).

Landesberg, R. et al., "The expression of the receptor for glycation endproducts (RAGE) in oral squamous cell carcinomas", Oral Surgery Oral Medicine Oral Pathology Oral Radiology, vol. 105, issue 5, pp. 617-624, (2008).

Zhou, H.W., "Recovery of function in osteoarthritic chondrocytes induced by $p16^{INK4a}$-specific siRNA in vitro", Rheumatology, vol. 43, pp. 555-568, (2004).

Fuijkschot, W.W. et al., "Prevention of age-induced N(ϵ)-(carboxymethyl)lysine accumulation in the microvasculature", European Journal of Clinical Investigation, vol. 46, issue 4, pp. 334-341, 12016). (Abstract Only).

Rasheed, Z.A. et al., "Pathology of pancreatic stroma in PDAC", Pancreatic Cancer and Tumor Microenvironment, pp. 1-10, (2012).

Morton, J.P. et al., "Mutant p53 drives metastasis and overcomes growth arrest/senescence in pancreatic cancer", PNAS, vol. 107, No. 1, pp. 246-251, (2010).

Verzijl, N. et al., "AGEing and osteoarthritis: a different perspective", Current Opinion in Rheumatology, vol. 15, issue 5, pp. 616-622, (2003).

Frescas, D. et al., "Senescent cells expose and secrete an oxidized form of membrane-bound vimentin as revealed by a natural polyreactive antibody", PNAS, vol. 114, No. 9, pp. E1668-E1677, (2017).

Oren, M. et al., "Mutant p53 gain-of-function in cancer", Cold Spring Harbor Perspectives in Biology, vol. 2, pp. 1-15, (2010).

"Senescence promotes chemotherapy side effects and cancer relapse", Medical Xpress, pp. 1-4, found at https://m.medicalxpress.com/news/2017-01-senescence-chemotherapy-side-effects-cancer.html, (2017).

Oh, J. et al., "Local clearance of senescent cells attenuates the development of post-traumatic osteoarthritis and creates a pro-regenerative environment", Nature Medicine, vol. 23, No. 6, pp. 1-9, (2017).

Protocols for "Isolation of untouched human T cells from peripheral blood mononuclear cells (PBMC)", Thermo Fisher Scientific, pp. 1-4, found at www.thermofishercom/us/en/home/references/protocols/proteins-expression-isolation-and-analysis/cell-separation-methods/human-cell-separation-protocols/isolation-of-untouched-human-t-cells-.html, printed on Aug. 17, 2017.

Henrich, C.J. et al., "Isolation and characterization of a glycopeptide from human senescent erythrocytes", Carbohydrate Research, vol. 120, pp. 55-66, (1983).

Yang, S. et al., "Impact of oxidative stress biomarkers and carboxymethyllysine (an advanced glycation end product) on prostate cancer: A prospective study", Clinical Genitourinary Cancer, vol. 13, No. 5, pp. 1-14, (2015).

Tsai, K.K.C. et al., "Low-dose radiation-induced senescent stromal fibroblasts render nearby breast cancer cells radioresistant", Radiation Research, vol. 172, pp. 306-313, (2009).

Nie, H et al., "Impaired glial glutamate uptake induces extrasynaptic glutamate spillover in the spinal sensory synapses of neuropathic rats", Journal of Neurophysiology, vol. 103, pp. 2570-2580, (2010).

Garcia-Matas, S. et al., "Dysfunction of astrocytes in senescence-accelerated mice SAMP8 reduces their neuroprotective capacity", Aging Cell, vol. 7, pp. 630-640, (2008).

Danysz, W. et al., "Alzheimer's disease, β-amyloid, glutamate, NMDA receptors and memantine-searching for the connections", British Journal of Pharmacology, vol. 167, pp. 324-352, (2012).

Blasko, I. et al., "Glial cells: Astrocytes and oligodendrocytes during normal brain aging", Encyclopedia of Neuroscience, pp. 743-747, (2009).

Leonard, B.W. et al., "Subventricular zone neural progenitors from rapid brain autopsies of elderly subjects with and without neurodegenerative disease", The Journal of Comparative Neurology, vol. 515, pp. 269-294, (2009).

Louveau, A. et al., "Structural and functional features of central nervous system lymphatic vessels", Nature, vol. 523, issue 7560, pp. 337-341, (2015).

Torgan, C., "Lymphatic vessels discovered in central nervous system", NIH Research Matters, pp. 1-4, found at www.nih.gov/news-events/nih-research-matters/lymphatic-vessels-discovered-central-nervous-system, Jun. 15, 2015.

(56) **References Cited**

OTHER PUBLICATIONS

Boskovitz, A. et al., "Monoclonal antibodies for brain tumour treatment", Expert Opinion on Biological Therapy, vol. 4, No. 9, pp. 1453-1471, (2004).

Takami, A. et al., "Treatment of primary central nervous system lymphoma with induction of complement-dependent cytotoxicity by intraventricular administration of autologous-serum-supplemented rituximab", Cancer Science, vol. 97, No. 1, pp. 80-83, (2006).

Biran, A. et al., "Senescent cells communicate via intercellular protein transfer", Genes & Development, vol. 29, pp. 791-802, (2015).

Golde, T.E. et al., "Proteinopathy-induced neuronal senescence: a hypothesis for brain failure in Alzheimer's and other neurodegenerative diseases", Alzheimer's Research & Therapy, vol. 1, No. 2, pp. 1-12, (2009).

Ouroboros, "Sweet madness: Sporadic prion disease and age-related changes in protein glycosylation", Research in the Biology of Aging, pp. 1-4, found at https://ouroboros.wordpress.com/2006/12/14/sweet-madness-sporadic-prion-disease-and-age-related-changes-in-protein-glycosylation/, (2006).

Xellbiogene, "Amyotrophic lateral sclerosis, immunotherapy is offering some hope", Xellbiogene.com, pp. 1-3, (2014).

Definition of "Complement system" printed from Wikipedia, the free encyclopedia on Aug. 4, 2015 found at http://en.wikipedia.org/wiki/Complement_system.

Definition of "Ventricular system" printed from Wikipedia, the free encyclopedia on Oct. 30, 2017 found at http://en.wikipedia.org/wiki/Ventricular_system.

Urushitani, M., "Future perspectives of immunotherapy against ALS", Rinsho Shinkeigaku, vol. 49, No. 11, pp. 818-820, (2009). (Abstract Only).

Cabezas, I.L. et al., "The role of glial cells in Alzheimer disease: potential therapeutic implications", Neurologia, vol. 29, No. 5, pp. 305-309, (2014).

Definition of "Prion" printed from Wikipedia, the free encyclopedia on Nov. 17, 2015 found at http://en.wikipedia.org/wiki/Prion.

"Prion Diseases", National Institute of Allergy and Infectious Diseases, pp. 1-2, found at www.niaid.nih.gov/diseases-conditions/prion-diseases, printed on Oct. 30, 2017.

"Alzheimer basics: Plaques and tangles", ALZ.org, pp. 1-2, found at www.alz.org/norcal/in_my_community_20545.asp, printed on Nov. 17, 2015.

Definition of "Lewy body" printed from Wikipedia, the free encyclopedia on Nov. 17, 2015 found at http://en.wikipedia.org/wiki/Lewy_body.

Definition of "Myocyte" printed from Wikipedia, the free encyclopedia on Nov. 17, 2015 found at http://en.wikipedia.org/wiki/Myocyte.

Definition of "Myosatellite cell" printed from Wikipedia, the free encyclopedia on Nov. 17, 2015 found at http://en.wikipedia.org/wiki/Myosatellite_cell.

Definition of "Microglia" printed from Wikipedia, the free encyclopedia on Oct. 30, 2017 found at http://en.wikipedia.org/wiki/Microglia.

Definition of "Astrocyte" printed from Wikipedia, the free encyclopedia on Oct. 30, 2017 found at http://en.wikipedia.org/wiki/Astrocyte.

Ouroboros, "A role for microglial senescence in Alzheimer's?", Research in the Biology of Aging, pp. 1-3, found at https://ouroboros.wordpress.com/?s=a+role+for+microgfial, (2007).

Chen, K.S. et al., "Monoclonal antibody therapy for malignant glioma", Glioma: Immunotherapeutic Approaches, chapter 10, pp. 121-141, (2012).

Reardon, S., "Alzheimer's drug sneaks through blood-brain barrier", Nature News, pp. 1-4, (2014).

"Astrocytes as a novel target in Alzheimer's disease", Expertsvar, pp. 1-2, (2012).

Myslinski, N., "Alzheimer's disease and the blood-brain barrier", Today's Geriatric Medicine, vol. 7, No. 1, pp. 1-10, (2014).

Hutter-Saunders, J.A.L. et al., "Pathways towards an effective immunotherapy for Parkinson's disease", Expert Reviews in Neurotherapeutics, vol. 11, No. 12, pp. 1703-1715, (2011).

Definition of "Intrathecal administration" printed from Wikipedia, the free encyclopedia on Oct. 30, 2017 found at http://en.wikipedia.org/wiki/Intrathecal_administration.

"What is ALS?", ALSA.org, found at www.alsa.org/2015-non-responsive-pp./about-als/what-is-als.html, printed on Mar. 31, 2016.

Rouger, K. et al., "Systemic delivery of allogenic muscle stem cells induces long-term muscle repair and clinical efficacy in Duchenne muscular dystrophy dogs", The American Journal of Pathology, vol. 179, No. 5, pp. 2501-2518, (2011).

Anderson, J.L. et al., "Brain function in Duchenne muscular dystrophy", Brain, vol. 125, pp. 4-13, (2002).

Jarius, S. et al., "AQP4 antibodies in neuromyelitis optica: diagnostic and pathogenetic relevance", Nature Reviews, vol. 6, pp. 383-392, (2010).

Wesolowski, J. et al., "Single domain antibodies: promising experimental and therapeutic tools in infection and immunity", Medical Microbiology and Immunology, vol. 198, pp. 157-174, (2009).

Definition of "Antibody" printed from Wikipedia, the free encyclopedia on Sep. 21, 2015 found at http://en.wikipedia.org/wiki/Antibody.

Definition of "Antibody-dependent cell-mediated cytotoxicity" printed from Wikipedia, the free encyclopedia on Dec. 28, 2015 found at http://en.wikipedia.org/wiki/Antibody-dependent_cell-mediated_cytotoxicity.

Definition of "Blocking antibody" printed from Wikipedia, the free encyclopedia on Dec. 28, 2015 found at http://en.wikipedia.org/wiki/Blocking_antibody.

Definition of "Fc receptor" printed from Wikipedia, the free encyclopedia on Dec. 28, 2015 found at http://en.wikipedia.org/wiki/Fc_receptor.

Definition of "Fragment crystallizable region" printed from Wikipedia, the free encyclopedia on Dec. 28, 2015 found at http://en.wikipedia.org/wiki/Fragment_crystallizable_region.

Definition of "Neutralizing antibody" printed from Wikipedia, the free encyclopedia on Dec. 28, 2015 found at http://en.wikipedia.org/wiki/Neutralizing_antibody.

Company Information on "NantKwest", pp. 1-4, found at www.nantkwest.com, printed on Apr. 1, 2016.

International Search Report dated Jul. 21, 2009 for PCT application No. PCT/US2009/44951.

Lindsey, J.B. et al., "Receptor for advanced glycation end-products (RAGE) and soluble RAGE (sRAGE): Cardiovascular implications", Diabetes Vascular Disease Research, vol. 6, No. 1, pp. 7-14, (2009).

Ando, K. et al., "Membrane proteins of human erythrocytes are modified by advanced glycation end products during aging in the circulation", Biochemical and Biophysical Research Communications, vol. 258, pp. 123-127, (1999).

Jandeleit-Dahm, K. et al., "The AGE/RAGE axis in diabetes-accelerated atherosclerosis", Clinical and Experimental Pharmacology and Physiology, vol. 35, pp. 329-334, (2008).

Sakata, N. et al., "Immunohistochemical localization of different epitopes of advanced glycation end products in human atherosclerotic lesions", Atherosclerosis, vol. 141, pp. 61-75, (1998).

Karachalias, N. et al., "Accumulation of fructosyl-lysine and advanced glycation end products in the kidney, retina and peripheral nerve of streptozotocin-induced diabetic rats", Biochemical Society Transactions, vol. 31, pp. 1423-1425, (2003).

Aroian, R. et al., "Pore-forming toxins and cellular non-immune defenses (CNIDs)", Current Opinion in Microbiology, vol. 10, pp. 57-61, (2007).

Dobson, J., "A twist on tumour targeting", Nature Materials, vol. 9, pp. 95-96, (2010).

Gutensohn, K. et al., "Extracorporeal plateletpheresis induces the interaction of activated platelets with white blood cells", Vox Sanguinis, vol. 78, No. 2, pp. 101-105, (2000).

Horiuchi, S. et al., "Immunochemical approach to characterize advanced glycation end products of the maillard reaction", The Journal of Biological Chemistry, vol. 266, No. 12, pp. 7329-7332, (1991).

(56) **References Cited**

OTHER PUBLICATIONS

Soetanto, K. et al., "Fundamental examination of cattle red blood cells damage with ultrasound exposure microscopic system (UEMS)", Japanese Journal of Applied Physics, vol. 37, part 1, No. 5B, pp. 3070-3073, (1998).

Harja, E. et al., "Vascular and inflammatory stresses mediate atherosclerosis via RAGE and its ligands in apoE-/- mice", The Journal of Clinical Investigation, vol. 118, No. 1, pp. 183-194, (2008).

Carstensen, E.L. et al., "Lysis of erythrocytes by exposure to cw ultrasound", Ultrasound in Medicine and Biology, vol. 19, No. 2, pp. 147-165, (1993).

Miller, M.W. et al., "Comparative sensitivity of human erythrocytes and lymphocytes to sonolysis by 1-MHz ultrasound", Ultrasound in Medicine and Biology, vol. 23, No. 4, pp. 635-638, (1997).

Iwata, H. et al., "Effect of carbonyl compounds on red blood cells deformability", Biochemical and Biophysical Research Communications vol. 321, pp. 700-706, (2004).

Schmitt, A. et al., "The binding of advanced glycation end products to cell surfaces can be measured using bead-reconstituted cellular membrane proteins", Biochimica et Biophysica Acta, vol. 1768, pp. 1389-1399, (2007).

Self-Medlin, Y. et al., "Glucose promotes membrane cholesterol crystalline domain formation by lipid peroxidation", Biochimica et Biophysica Acta, vol. 1788, pp. 1398-1403, (2009).

Singh, N. et al., "The PPAR-γ activator, rosiglitazone, inhibits actin polymerisation in monocytes: involvement of Akt and intracellular calcium", Biochemical and Biophysical Research Communications, vol. 333, pp. 455-462, (2005).

Li, Y-M. et al., "Effects of high glucose on mesenchymal stem cell proliferation and differentiation", Biochemical and Biophysical Research Communications, vol. 363, pp. 209-215, (2007).

Takata, K. et al., "Endocytic uptake of nonenzymatically glycosylated proteins is mediated by a scavenger receptor for aldehyde-modified proteins", The Journal of Biological Chemistry, vol. 263, No. 29, pp. 14819-14825, (1988).

Mi, Y. et al., "Apoptosis in leukemia cells is accompanied by alterations in the levels and localization of nucleolin", Journal of Biological Chemistry, vol. 278, pp. 8572-8579, (2003).

Christian, S. et al., "Nucleolin expressed at the cell surface is a marker of endothelial cells in angiogenic blood vessels", Journal of Cell Biology, vol. 163, No. 4, pp. 871-878, (2003).

Loo, T.W. et al., "Identification of residues in the drug translocation pathway of the human multidrug resistance P-glycoprotein by arginine mutagenesis", Journal of Biological Chemistry, vol. 284, No. 36, pp. 24074-24087, (2009).

Brundin, P. et al., "Prion-like transmission of protein aggregates in neurodegenerative diseases", Nature Reviews Molecular Cell Biology, vol. 11, No. 4, pp. 301-307, (2010).

Perez, C. et al., "Translational control of the abundance of cytoplasmic poly(A) binding protein in human cytomegalovirus-infected cells", Journal of Virology, vol. 85, No. 1, pp. 156-164, (2011).

Persson, J. et al., "Interleukin-lbeta and tumour necrosis factor-alpha impede neutral lipid turnover in macrophage-derived foam cells", BMC Immunology, vol. 9, No. 70, pp. 1-11, (2008).

Vergne, I. et al., "Cell biology of mycobacterium tuberculosis phagosome", Annu. Rev. Cell Dev. Biology, vol. 20, pp. 367-394, (2004).

Moskowitz, S.M. et al., "The role of pseudomonas lipopolysaccharide in cystic fibrosis airway Infection", Subcell Biochemistry, vol. 53, pp. 241-253, (2010).

Hall-Stoodley, L. et al., "Direct detection of bacterial biofilms on the middle-ear mucosa of children with chronic otitis media", JAMA, vol. 296, No. 2, pp. 202-211, (2006).

Franke-Fayard, B. et al., "Sequestration and tissue accumulation of human malaria parasites: Can we learn anything from rodent models of malaria?", PLoS Pathogens, vol. 6, issue 9, pp. 1-10, e1001032, (2010).

Zhang, S. et al., "Delineation of diverse macrophage activation programs in response to intracellular parasites and cytokines", PLoS Neglected Tropical Diseases, vol. 4, No. 3, e648 (2010).

Ma, Y. et al., "NS3 helicase domains involved in infectious intracellular hepatitis C virus particle assembly", Journal of Virology, vol. 82, No. 15, pp. 7624-7639, (2008).

Korant, B.D. et al., "Inhibition by zinc of rhinovirus protein cleavage: interaction of zinc with capsid polypeptides", Journal of Virology, vol. 18, No. 1, pp. 298-306, (1976).

Ameli, S. et al., "Effect of immunization with homologous LDL and oxidized LDL on early atherosclerosis in hypercholesterolemic rabbits", Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 16, pp. 1074-1079, (1996).

Nilsson, J. et al., "Inflammation and immunity in diabetic vascular complications", Current Opinion in Lipidology, vol. 19, issue 5, pp. 519-524, (2008).

Schiopu, A. et al., "Recombinant antibodies to an oxidized low-density lipoprotein epitope induce rapid regression of atherosclerosis in apobec-1^{-1-}/low-density lipoprotein receptor$^{-/-}$mice", Journal of the American College of Cardiology, vol. 50, No. 24, pp. 2313-2318, (2007).

Schiopu, A. et al., "Recombinant human antibodies against aldehyde-modified apolipoprotein B-100 peptide sequences inhibit atherosclerosis", Circulation, vol. 110, pp. 2047-2052, (2004).

Bassirat, M. et al., "Short- and long-term modulation of microvascular responses in streptozotocin-induced diabetic rats by glycosylated products", Journal of Diabetes and its Complications, vol. 24, pp. 64-72, (2010).

Ge, J. et al., "Advanced glycosylation end products might promote atherosclerosis through inducing the immune maturation of dendritic cells", Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 25, pp. 2157-2163, (2005).

Gugliucci, A. et al., "Circulating advanced glycation peptides in streptozotocin-induced diabetic rats: evidence for preferential modification of IgG light chains", Life Sciences, vol. 62, No. 23, pp. 2141-2150, (1998).

Pullerits, R. et al., "Synovial fluid expression of autoantibodies specific for RAGE relates to less erosive course of rheumatoid arthritis", Rheumatology, vol. 46, pp. 1367-1371, (2007).

Bro, S. et al., "A neutralizing antibody against receptor for advanced glycation end products (RAGE) reduces atherosclerosis in uremic mice", Atherosclerosis, vol. 201, pp. 274-280, (2008).

Turk, Z. et al., "Detection of autoantibodies against advanced glycation endproducts and AGE-immune complexes in serum of patients with diabetes mellitus", Clinica Chimica Acta, vol. 303, pp. 105-115, (2001).

Li, M. et al., "Glycan changes: cancer metastasis and anti-cancer vaccines", Journal of Biosciences, vol. 35, No. 4, pp. 665-673, (2010).

Kyte, J.A. et al., "Third international conference on cancer vaccines/adjuvants/delivery for the next decade (CVADD 2009)", Expert Reviews Vaccines, vol. 9, No. 2, pp. 119-123, (2010).

Akbulut, H. et al., "Chemotherapy targeted to cancer tissue potentiates antigen-specific immune response induced by vaccine for in vivo antigen loading and activation of dendritic cells", Molecular Therapy, vol. 16, No. 10, pp. 1753-1760, (2008).

Li, Y.M. et al., "Glycation products in aged thioglycollate medium enhance the elicitation of peritoneal macrophages", Jounal of Immunological Methods, vol. 201, issue 2, pp. 183-188, (1997).

Poggioli, S. et al., "Age-related increase of protein glycation in peripheral blood lymphocytes is restricted to preferential target proteins", Experimental Gerontology, vol. 37, issue 10-11, pp. 1207-1215, (2002).

Poggioli, S. et al., "Evidence of preferential protein targets for age-related modifications in peripheral blood lymphocytes", Annals of the New York Academy of Sciences, vol. 1019, issue 1, pp. 211-214, (2004).

Dominaitiene, R. et al., "Effects of differently oxidized LDL on the expression of pro-inflammatory molecules in human monocytes in vitro", In Vitro and Molecular Toxicology, vol. 14, No. 2, pp. 83-97, (2001).

(56) **References Cited**

OTHER PUBLICATIONS

Jiang, Z-H. et al., "Synthetic vaccines: the role of adjuvants in immune targeting", Current Medicinal Chemistry, vol. 10, No. 15, pp. 1423-1439, (2003).
Buskas, T. et al , "Immunotherapy for cancer. Synthetic carbohydrate-based vaccines", Chemical Communications, Issue 36, pp. 5335-5349, (2009).
Cohen, M.P. et al., "Amelioration of diabetic nephropathy by treatment with monoclonal antibodies against glycated albumin", Kidney International, vol. 45, pp. 1673-1679, (1994).
Davis, P.J. et al., "How can thermal processing modify the antigenicity of proteins?", Allergy, vol. 56, supplemental 67, pp. 56-60, (2001).
Koga, M. et al. "Clinical impact of glycated albumin as another glycemic control marker", Endocrine Journal, vol. 57, No. 9, pp. 751-762, (2010).
Shcheglova, T. et al., "Reactive immunization suppresses advanced glycation and mitigates diabetic nephropathy", Journal of the American Society of Nephrology, vol. 20, No. 5, pp. 1012-1019, (2009).
Virella, G. et al., "Autoimmune response to advanced glycosylation end-products of human LDL", Journal of Lipid Research, vol. 44, pp. 487-493, (2003).
Ihssen, J. et al., "Production of glycoprotein vaccines in *Escherichia coli*", Microbial Cell Factories, vol. 9, No. 61, pp. 1-13, (2010).
Habets, K.L.L. et al., "Vaccination using oxidized low-density lipoprotein-pulsed dendritic cells reduces atherosclerosis in LDL receptor-deficient mice", Cardiovascular Research, vol. 85, pp. 622-630, (2010).
Mironova, R. et al., "Glycation and post-translational processing of human interferon-γ expressed in *Escherichia coli*", The Journal of Biological Chemistry, vol. 278, No. 51, pp. 51068-51074, (2003).
Vogel, F.R. et al., "A compendium of vaccine adjuvants and excipients", Pharmaceutical Biotechnology, vol. 6, pp. 141-228, (1995).
Monograph series, World Health Organization, "Methods of Vaccine Production", part 4, chapters 18-29, pp. 189-267, (1973).
Cohen, M.P. et al., "Prevention of diabetic nephropathy in db/db mice with glycated albumin antagonists: A novel treatment strategy", The Journal of Clinical Investigation, vol. 95, pp. 2338-2345, (1995).
Naka, Y. et al., "RAGE Axis, Animal models and novel insights into the vascular complications of diabetes", Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 24, pp. 1342-1349, (2004).
European Search Report dated Nov. 8, 2011 for PCT application No. PCT/US2009/044951.
Bierhaus, A. et al., "AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept", Cardiovascular Research, vol. 37, No. 3, pp. 586-600, (1998).
Murphy, J.F. "Trends in cancer immunotherapy", Clinical Medicine Insights: Oncology, vol. 4, pp. 67-80, (2010).
Beier, K.C., "Master switches of T-cell activation and differentiation", European Respiratory Journal, vol. 29, pp. 804-812, (2007).
Schmidlin, H., "New insights in the regulation of human B cell differentiation", Trends in Immunology, vol. 30, No. 6, pp. 277-285, (2009).
Coler, R.N. et al., "Development and characterization of synthetic glucopyranosyl lipid adjuvant system as a vaccine adjuvant", PLoS One, vol. 6, No. 1, e16333, pp. 1-12, (2011).
Cheadle, E.J., "Bugs as drugs for cancer", Immunology, vol. 107, pp. 10-19, (2002).
The Pink Book, Epidemiology and Prevention of vaccine preventable diseases, 11th Ed., pp. B7-B13, (2009), Found at www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-1.pdf.
The Pink Book, Epidemiology and Prevention of vaccine preventable diseases, 11th Ed., 4 pages, (2009), Found at www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf.
Book Reviews, International Microbiology, vol. 7, pp. 291-295, (2004).
"Glycation: How eating sugar causes wrinkles", www.brighthub.com/health/diet-nutrition/articles/18410.aspx, 1 page, published Oct. 8, 2009.
Ellis, G., "The myth of the glycemic index and its child: good carbs-bad carbs", Targeted Body Systems, www.targetedbodysystems.com/tag/low-carb-diet-plans/, pp. 1-5, published Feb. 16, 2009.
"Diabetic glycation and inflammation—what diabetes does to your coronary arteries", www.rebelheartsurgeon-antioxidants.net/diabetic-glycation.html, pp. 1-9, downloaded Aug. 17, 2010.
Dziarski, R., "Cell-bound albumin is the 70-kDa peptidoglycan-, lipopolysaccharide-, and lipoteichoic acid-binding protein on lymphocytes and macrophages", The Journal of Biological Chemistry, vol. 269, No. 32, pp. 20431-20436, (1994).
Peters Jr. T.,"5-Metabolism: Albumin in the body", All About Albumin Biochemistry, Genetics, and Medical Applications, Chapter 5, pp. 188-250, (1995).
Vlassara, H. et al., "High-affinity-receptor-mediated uptake and degradation of glucose-modified proteins: A potential mechanism for the removal of senescent macromolecules", Proceeding of the National Academy of Science, USA, Biochemistry, vol. 82, pp. 5588-5592, (1985).
Wade, N., "Purging cells in mice is found to combat aging ills", New York Times, found at NYTimes.com, pp. 1-3, (2011).
Roll, P. et al., "Anti-CD20 therapy in patients with rheumatoid arthritis", Arthritis & Rheumatism, vol. 58, No. 6, pp. 1566-1575, (2008).
Kajstura J. et al., "Myocyte turnover in the aging human heart", Circulation Research, vol. 107, pp. 1374-1386, (2010).
Baker, D.J. et al., "Clearance of p161nk4a-positive senescent cells delays ageing-associated disorders", Nature, vol. 479, pp. 232-236, (2011).
Breyer, V. et al., "Intracellular glycation of nuclear DNA, mitochondrial DNA, and cytosolic proteins during senescence-like growth arrest", DNA Cell Biology, vol. 30, No. 9, pp. 681-689, (2011).
Ravelojaona, V. et al., "Expression of senescence-associated beta-galactosidase (SA-beta-Gal) by human skin fibroblasts, effect of advanced glycation end-products and fucose or rhamnose-rich polysaccharides", Archives of Gerontology and Geriatrics, vol. 48, issue 2, pp. 151-154, (2009).
International Search Report dated Apr. 26, 2012 for PCT application No. PCT/US2011/053399.
International Search Report dated Jun. 13, 2012 for PCT application No. PCT/US2011/061387.
Wautier, J. -L. et al., "Advanced glycation end products (AGEs) on the surface of diabetic erythrocytes bind to the vessel wall via a specific receptor inducing oxidant stress in the vasculature: a link between surface-associated AGEs and diabetic complications", Proc. Natl. Acad. Sci. USA, vol. 91, No. 16, pp. 7742-7746, (1994).
Siegel, R. J. et al., "Ultrasonic plaque ablation: A new method for recanalization of partially or totally occluded arteries", Circulation, vol. 78, No. 6, pp. 1443-1448, (1988).
International Search Report dated Jun. 27, 2012 for PCT application No. PCT/US2012/031446.
Immuno, Catalog No. 637061, 637062, "Mouse, anti-age (advanced glycation end products), monoclonal antibody", http://www.mpbio.com/detailed_info.php?family_key=0863706, 2 pages, accessed Jul. 26, 2012.
Ahmed, E. K. et al., "Protein modification and replicative senescence of WI-38 human embryonic fibroblasts", Aging Cell, vol. 9, pp. 252-272, (2010).
Vlassara, H. et al, "Advanced glycosylation endproducts on erythrocyte cell surface induce receptor-mediated phagocytosis by macrophages", J. Exp. Med., The Rockefeller University Press, vol. 166, pp. 539-549, (1987).
Yang, Z. et al., "Two novel rat liver membrane proteins that bind advanced glycosylation endproducts: Relationship to macrophage receptor for glucose-modified proteins", J. Exp. Med., The Rockefeller University Press, vol. 174, pp. 515-524, (1991).
Vlassara, H. et al, "Advanced glycation endproducts promote adhesion molecule (VCAM-1, ICAM-1) expression and atheroma formation in normal rabbits", Molecular Medicine, vol. 1, No. 4. pp. 447-456, (1995).

(56) **References Cited**

OTHER PUBLICATIONS

Vaysse, J. et al., "Adhesion and erythrophagocytosis of human senescent erythrocytes by autologous monocytes and their inhibition by β-galactosyl derivatives", Proc. Natl. Acad. Sci. USA, Cell Biology, vol. 83, pp. 1339-1343, (1986).

Li, Y. M. et al., "Prevention of cardiovascular and renal pathology of aging by the advanced glycation inhibitor aminoguanidine", Proc. Natl. Acad. Sci. USA, Medical Sciences, vol. 93, pp. 3902-3907, (1996).

Manesso, E. et al., "Dynamics of β-cell turnover: evidence for β-cell turnover and regeneration from sources of β-cells other than β-cell replication in the HIP rat", American Journal of Physiology Endocrinology and Metabolism, vol. 297, pp. E323-E330, (2009).

Stepanov, A.V. et al., "Design of targeted B cell killing agents", PLoS ONE, vol. 6, issue 6, e20991, pp. 1-10, (2011).

Fact Sheet, "Targeted Cancer Therapies", www.cancer.gov/cancertopics/factsheet/Therapy/Fs7_49.pdf, pp. 1-8, (2012).

Kay, M.M. "Generation of senescent cell antigen on old cells initiates IgG binding to a neoantigen", Cellular and Molecular Biology (Noisy-le-Grand, France), vol. 39, No. 2, pp. 131-153, (1993), Abstract Only.

Cirocchi, R. et al., "Meta-analysis of thyroidectomy with ultrasonic dissector versus conventional clamp and tie", World Journal of Surgical Oncology, vol. 8, No. 112, pp. 1-7, (2010).

Lingeman, J.E. et al., "Current perspective on adverse effects in shock wave lithotripsy", White Paper, American Urological Association Education and Research, found at www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/whitepaper.pdf, 17 pages, (2009).

De Groot, K. et al., "Vascular endothelial damage and repair in antineutrophil cytoplasmic antibody associated vasculitis", Arthritis & Rheumatism, vol. 56, No. 11, pp. 3847-3853, (2007).

Imani, F. et al., "Advanced glycosylation endproduct-specific receptors on human and rat t-lymphocytes mediate synthesis of interferon γ: role in tissue remodeling", J. Exp. Med., vol. 178, pp. 2165-2172, (1993).

Kirstein, M. et al., "Receptor-specific induction of insulin-like growth factor I in human monocytes by advanced glycosylation end product-modified proteins", J. Clin. Invest., vol. 90, pp. 439-446, (1992).

Le Grand, F. et al., "Skeletal muscle satellite cells and adult myogenesis", Curr. Opin. Cell Biology, vol. 19, No. 6, pp. 628-633, (2007).

Sasaki, M. et al., "Mesenchymal stem cells are recruited into wounded skin and contribute to wound repair by transdifferentiation into multiple skin cell type", The Journal of Immunology, vol. 180, pp. 2581-2587, (2008).

Misur, I. et al., "Advanced glycation endproducts in peripheral nerve in type 2 diabetes with neuropathy", Acta Diabetol, vol. 41, pp. 158-166, (2004).

Saltykov, B.B., "Mechanisms of development of diabetic macroangiopathy", Arkh Patol vol. 63, No. 2, pp. 21-26, (2001), Abstract Only.

Grossin, N. et al., "Red blood cell adhesion in diabetes mellitus is mediated by advanced glycation end product receptor and is modulated by nitric oxide", Biorheology, vol. 46, No. 1, pp. 63-72, (2009).

Liang, Y. et al., "Rituximab for children with immune thrombocytopenia: A systematic review", PLoS ONE, vol. 7, issue 1, pp. 1-11, (2012).

Fehrenbach, H. et al., "Up-regulated expression of the receptor for advanced glycation end products in cultured rat hepatic stellate cells during transdifferentiation to myofibroblasts", Hepatology, vol. 34, No. 5, pp. 943-952, (2001).

Agostini, A. et al., "Targeted cargo delivery in senescent cells using capped mesoporous silica nanoparticles", Angewandte Chemie International Edition, vol. 51, pp. 10556-10560, (2012).

Larson, R.A. et at., "Tumor lysis syndrome: Definition, pathogenesis, clinical manifestations, etiology and risk factors", found at www.uptodate com/contents/tumor-lysis-syndrome-definition-pathogenesis-clinical-manifestations-etiology-and-risk-factors?detectedLanguage=en&source=search_result&search=tumor+lysis+syndrome&selectedTitle=2-69&provider=noProvider, pp. 1-4, printed on Jun. 11, 2013.

Hansel, T.T. et al "The safety and side effects of monoclonal antibodies", Nature Reviews, vol. 9, pp. 325-337, (2010).

Nass, N. et al., "Advanced glycation end products, diabetes and ageing", Zeitschrift fur Gerontologie and Geriatrie, vol. 40, issue 5, pp. 349-356, (2007).

Wautier, J-L. et al., Protein Glycation: "A firm link to endothelial cell dysfunction", Circulation Research, Journal of the American Heart Association, vol. 95, pp. 233-238, (2004).

Meuter, A. et al., "Markers of cellular senescence are elevated in murine blastocysts cultured in vitro: molecular consequences of culture in atmospheric oxygen", Journal of Assisted Reproduction and Genetics, vol. 31, issue 10, pp. 1259-1267, (2014).

Freund, A. et al., "Inflammatory networks during cellular senescence: causes and consequences", Trends in Molecular Medicine, vol. 16, No. 5, pp. 238-246, (2010).

Hadrabová, J. et al., "Chicken immunoglobulins for prophylaxis: Effect of inhaled antibodies on inflammatory parameters in rat airways", Journal of Applied Biomedicine, 4 pages, Available online May 5, 2014.

Ferraccioli, G. et al., "Interleukin-1β and Interleukin-6 in arthritis animal models: Roles in the early phase of transition from acute to chronic inflammation and relevance for human rheumatoid arthritis", Molecular Medicine, vol. 16, issue 11-12, pp. 552-557, (2010).

Zhao, Y. et al., "The bovine antibody repertoire", Developmental & Comparative Immunology, vol. 30, issues 1-2, pp. 175-186, (2006).

Wagner, B. et al., "The complete map of the Ig heavy chain constant gene region reveals evidence for seven IgG isotypes and for IgD in the horse", Journal of Immunology, vol. 173, No. 5, pp. 3230-3242, (2004).

Strietzel, C.J. et al., "In vitro functional characterization of feline IgGs", Veterinary Immunology and Immunopathology, vol. 158, issues 3-4, pp. 214-223, (2014).

Patel, M. et al., "Sequence of the dog immunoglobulin alpha and epsilon constant region genes", Immunogenetics, vol. 41, issue 5, pp. 282-286, (1995).

Maass, D.R. et al., "Alpaca (*Lama pacos*) as a convenient source of recombinant camelid heavy chain antibodies (VHHs)", Journal of Immunology Methods, vol. 324, issues 1-2, pp. 13-25, (2007).

European Search Report dated Sep. 12, 2014 for EP application No. EP14170802.4-1408.

Fessler, J. et al., "Senescent T cells promote bone loss in rheumatoid arthritis", Abstracts of the American College of Rheumatology/Association of Rheumatology Health Professionals, Annual Scientific Meeting, Washington, DC, Nov. 9-14, 2012, Arthritis & Rheumatism, vol. 64, supplement 10, p. 2312, (2012) found at http://blackwellpublishing.com/acrmeeting/abstract.asp?MeetingID=789&id=103040.

Weyand, C.M. et al., Abstract of "T-cell aging in rheumatoid arthritis", Current Opinion in Rheumatology, vol. 26, No. 1, pp. 93-100, (2014) found at http://www.ncbi.nlm.nih.gov/m/pubmed/24296720/.

Dvergsten, J. et al., "Prevalence of functionally active, senescent T cells in juvenile idiopathic arthritis", Abstracts of the American College of Rheumatology/Association of Rheumatology Health Professionals, Annual Scientific Meeting, Philadelphia, Oct. 16-21, 2009, Arthritis & Rheumatism, vol. 60, supplement 10, p. 1313, (2009), found at http://blackwellpublishing.com/acrmeeting/abstract.asp?MeetingID=761&id=80937.

Definition of "Dissociation constant" printed from Wikipedia, the free encyclopedia on Sep. 17, 2014 found at http://en.wikipedia.org/wiki/Dissociation_constant.

Sigma-Aldrich product specification of "Nα,Nα-Bis(carboxymethyl)-L-lysine trifluoroacetate salt ≥95% (TLC)", found at http://sigmaaldrich.com/catalog/product/sigma/c3205?lang=en&region=US, printed on Sep. 17, 2014.

"Pulmatrix demonstrates iSPERSE capabilities for inhaled dry powder delivery of antibiotics and antibodies", data presented at Respiratory Drug Delivery 2012, 3 pages, printed on Sep. 4, 2014,

(56) **References Cited**

OTHER PUBLICATIONS

found at http://businesswire.com/news/home/20120515005279/en/Pulmatrix-Demonstrates-iSPERSE-Capabilities-Inhaled-Dry-Powder#.VEgU4hauNbs.

Chan, A.C. et al., "Therapeutic antibodies for autoimmunity and inflammation", Nature Reviews Immunology, vol. 10, pp. 301-316, (2010).

Pradat, P.F. et al., "Abnormalities of satellite cells function in amyotrophic lateral sclerosis", Amyotrophic Lateral Sclerosis, vol. 12, No. 4, pp. 264-271, (2011).

Tchkonia, T. et al., "Cellular senescence and the senescent secretory phenotype: therapeutic opportunities", The Journal of Clinical Investigation, vol. 123, No. 3, pp. 966-972, (2013).

Kitada, K. et al., "Aldosterone induces p21-regulated apoptosis via increased synthesis and secretion of tumour necrosis factor-α in human proximal tubular cells", Clinical and Experimental Pharmacology and Physiology, vol. 39, No. 10, pp. 858-863, (2012).

Definition of "TNF inhibitor", printed from Wikipedia, the free encyclopedia on Oct. 4, 2014, 4 pages, found at http://en.wikipedia.org/wiki/TNF_inhibitor?oldid=628250399.

Definition of "Etanercept", printed from Wikipedia, the free encyclopedia on Aug. 24, 2014, 6 pages, found at http://en.wikipedia.org/wiki/Etanercept?oldid=622648157.

AbbVie, Inc., "Humira adalimumab: Learn about Humira", found at https://www.humira.com/rheumatoid-arthritis, 7 pages, printed on Aug. 11, 2014.

AbbVie, Inc., "Medication Guide for Humira", found at https://www.humira.com/rheumatoid-arthritis, 9 pages, printed on Aug. 11, 2014.

AbbVie, Inc., "Humira: A biologic that targets and helps block TNF-alpha", found at https://www.humira.com/rheumatoid-arthritis/how-humira-works-for-ra, 8 pages, printed on Aug. 11, 2014.

AbbVie, Inc., "How Humira (adalimumab) works video transcript", found at https://www.humira.com/rheumatoid-arthritis/how-humira-works-video-transcript, 5 pages, printed on Aug. 11, 2014.

AbbVie, Inc., "Humira and methotrexate—a combination that has demonstrated results", found at https://www.humira.com/rheumatoid-arthritis/humira-and-methotrexate, 7 pages, printed on Aug. 11, 2014.

Madhur, M.S. et al., "Senescent T cells and hypertension: New ideas about old cells", Hypertension, vol. 62, pp. 13-15, (2013).

James, P.E. et al., "Vasorelaxation by red blood cells and impairment in diabetes: Reduced nitric oxide and oxygen delivery by glycated hemoglobin", Circulation Research, vol. 94, pp. 976-983, (2004).

Shibayama, R. et al., "Autoantibody against N(epsilon)-(carboxymethyl)lysine: an advanced glycation end product of the Maillard reaction", Diabetes, vol. 48, No. 9, pp. 1842-1849, (1999).

Bumol, T.F. et al., "Monoclonal antibody and an antibody-toxin conjugate to a cell surface proteoglycan of melanoma cells suppress in vivo tumor growth", Proceeding of the National Academy of Science, vol. 80, pp. 529-533, (1983).

"AGEs (all species) antibody—Product Details", Antibodies Online, 4 pages, found at www.web.archive.org/web/20081229071154/http://www.antibodies-online.com/antibody/289931/AGEs+All+Species/, printed on Dec. 10, 2014.

"Antibody Engineering", Fusion Antibodies, 2 pages, found at www.web.archive.org/web/20080628225818/http://www.fusionantibodies.com/index.cfm/area/information/page/engineering?, printed on Dec. 16, 2014.

Hargreaves, R.E.G. et al., "Selective depletion of activated T cells: the CD4OL-specific antibody experience", Trends in Molecular Medicine, vol. 10, No. 3, pp. 130-135, (2004).

Leinenga, G. et al., "Scanning ultrasound removes amyloid-β and restores memory in an Alzheimer's disease mouse model", Science Translational Medicine, vol. 7, issue 278, pp. 1-11, (2015).

Peppa, M. et al., "Glucose, advanced glycation end products, and diabetes complications: What is new and what works", Clinical Diabetes, vol. 21, No. 4, pp. 186-187, (2003).

Lv, Y. et al., "Low-intensity ultrasound combined with 5-aminolevulinic acid administration in the treatment of human tongue squamous carcinoma", Cellular Physiology and Biochemistry, vol. 30, pp. 321-333, (2012).

Campisi, J. et al., "Cellular senescence: when bad things happen to good cells", Nature Reviews: Molecular Cell Biology, vol. 8, pp. 729-749, (2007).

"ALSUntangled No. 23: The Rife Machine and retroviruses", Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, vol. 15, pp. 157-159, (2014).

Roylance, D., "Mechanical properties of materials", pp. 1-128, (2008), available at www.web.mit.edu/course/3/3.225/book.pdf.

Vidarsson, G. et al., "IgG subclasses and allotypes: from structure to effector functions", Frontiers in Immunology, vol. 5, article 520, pp. 1-17, (2014).

Lin, H-T. et al., "Stem cell therapy: an exercise in patience and prudence", Philosophical Transactions of the Royal Society B: Biological Sciences 368, (2013).

Waldmann, T.A., "Immunotherapy:past, present and future", Nature Medicine, vol. 9, No. 3, pp. 269-277, (2003).

Okamoto, T. et al., "Advanced glycation end products induce angiogenesis in vivo", Microvascular Research, vol. 63, pp. 186-195, (20022.

Nagal, R. et al., "Application of monoclonal antibody libraries for the measurement of glycation adducts", Biochemical Society Transactions, vol. 31, part 6, pp. 1438-1440, (2003).

De Genst, E. et al., "Antibody repertoire development in camelids", Developmental and Comparative Immunology, vol. 30, pp. 187-198, (2006).

Griffin, L.M. et al., "Analysis of hevy and light chain sequences of conventional camelid antibodies from *Camelus dromedarius* and *Camelus bactrianus* species", Journal of Immunological Methods, vol. 405, pp. 35-46, (2014).

Hamers-Casterman, C. et al., "Naturally occurring antibodies devoid of light chains", Nature, vol. 363, pp. 446-448, (1993).

Muyldermans, S. et al., "Sequence and structure of V_H domain from naturally occurring camel heavy chain immunoglobulins lacking light chains", Protein Engineering, vol. 7, No. 9, pp. 1129-1135, (1994).

Nguyen, V. K. et al., "Camel heavy-chain antibodies: diverse germline VHH and specific mechanisms enlarge the antigen-binding repertoire", The EMBO Journal, vol. 19, No. 5, pp. 921-930, (2000).

Kirstein, et al., "Advanced protein glycosylation induces transendothelial human monocyte chemotaxis and secretion of platelet-derived growth factor: roll in vascular disease of diabetes and aging", PNAS, vol. 87, No. 22, pp. 9010-9014, (1990).

Invitation to Pay Additional Fees and Partial International Search Report dated Jan. 13, 2016 for PCT application No. PCT/US2015/050154.

Feldmann, M. et al., "Anti-TNFalpha therapy of rheumatoid arthritis: What have we learned?", Annual Review of Immunology, vol. 19, pp. 163-196, (2001).

Drinda, S. et al., "Identification of the advanced glycation end products N-carboxymethyllysine in the synovial tissue of patients with rheumatoid arthritis", Annals of the Rheumatic Diseases, vol. 61, No. 6, pp. 488-492, (2002).

Ahmad, S. et al., "Preferential recognition of epitopes on AGE-IgG by the autoantibodies in rheumatoid arthritis patients", Human Immunology, vol. 74, No. 1, pp. 23-27, (2013).

Johns, L.D., "Nonthermal effects of therapeutic ultrasound: The frequency resonance hypothesis", Journal of Athletic Training, vol. 37, No. 3, pp. 293-299, (2002).

Wang, B-L. et al., "Identification of monoclonal antibody of advanced glycation end products", Chinese Journal of Arteriosclerosis, vol. 14, No. 5, pp. 409-412, (2006).

Wang, J.C. et al., "Aging and Atherosclerosis mechanisms, functional consequences, and potential therapeutics for cellular senescence", Circulation Research, vol. 111, pp. 245-259, (2012).

Minamino, T. et al., "Vascular cell senescence contribution to Atherosclerosis", Circulation Research, vol. 100, pp. 15-26, (2007).

(56) **References Cited**

OTHER PUBLICATIONS

Isoda, K. et al., "Glycated Ldl increases monocyte CC chemokine receptor 2 expression and monocyte chemoattractant protein-1-mediated chemotaxis", Atherosclerosis, vol. 198, No. 2, pp. 307-312, (2008).

Roos, C.M. et al., "Chronic senolytic treatment alleviates established vasomotor dysfunction in aged or atherosclerotic mice", Aging Cell, 8 pages, (2016).

Hall, B.M. et al., "Aging of mice is associated with p16(Ink4a)- and β-galactosidase-positive macrophage accumulation that can be induced in young mice by senescent cells", Aging, vol. 8, No. 7, pp. 1-18, (2016).

Mera, K. et al., "An autoantibody against N^{ϵ}-(carboxyethyl)lysine (CEL): Possible involvement in the removal of CEL-modified proteins by macrophages", Biochemical and Biophysical Research Communications, vol. 407, pp. 420-425, (2011).

Reddy, S. et al., "N^{ϵ}-(Carboxymethyl)lysine is a dominant advanced glycation end product (AGE) antigen in tissueproteins", Biochemistry, vol. 34, pp. 10872-10878, (1995).

Katcher, H.L., "Studies that shed new light on aging", Biochemistry (Moscow), vol. 78, No. 9, pp. 1061-1070, (2013).

Naylor, R.M. et al., "Senescent Cells: A novel therapeutic target for aging and age-related diseases", Clinical Pharmacology & Therapeutics, vol. 93, No. 1, pp. 105-116, (2013).

Beaulieu, L-P. et al., "Inhibitory effect of the cree traditional medicine wiishichimanaanh (vaccinium vitis-idaea) on advanced glycation endproduct formation: identification of active principles", Phytotherapy Research, vol. 24, pp. 741-747, (2010).

Ulrich, P. et al., "Protein glycation, diabetes, and aging", Recent Progress in Hormone Research, vol. 56, pp. 1-21, (2000).

Van Heijst, J.W.J. et al., "Advanced glycation end products in human cancer tissues: detection of N^{ϵ}-(carboxymethyl)lysine and argpyrimidine", Annals of the New York Academy of Sciences, vol. 1043, pp. 725-733, (2005).

Fielding, R.A. et al., "Sarcopenia: An undiagnosed condition in older adults. Current consensus definition: Prevalence, etiology, and consequences", Journal of the American Medical Directors Association, vol. 12, No. 4, pp. 249-256, (2011).

Definition of "Sarcopenia", printed from Wikipedia, the free encyclopedia on Jul. 25, 2016, 5 pages, found at http://en.wikipedia.org/wiki/Sarcopenia.

"What is Sarcopenia?", International Osteoporosis Foundation, 2 pages, found at www.iofbonehealth.org/what-sarcopenia, (2014).

"Sarcopenia with aging", Webmd, 2 pages, found at www.webmd.com/healthy-aging/sarcopenia-with-aging, (2014).

Definition of "Keyhole limpet hemocyanin", printed from Wikipedia, the free encyclopedia on Jul. 25, 2016, 4 pages, found at https://en.wikipedia.org/wiki/Keyhole_limpet_hemocyanin.

Cell Biolabs, Inc., "CML-BSA Product Data Sheet", 3 pages, found at http://www.cellbiolabs.com/sites/default/files/STA-314-cml-bsa.pdf, (2010).

Cell Biolabs, Inc., "CML (N-epsilon-(Caboxymethyl)Lysine) Assays and Reagents", 1 page, found at http://www.cellbiolabs.com/cml-assays, (2014).

Cruz-Jentoft, A.J. et al., "Sarcopenia: European consensus on definition and diagnosis", Age and Ageing, vol. 39, pp. 412-423, (2010).

Rolland, Y. et al., "Sarcopenia: Its assessment, etiology, pathogenesis, consequences and future perspectives", The Journal of Nutrition, Health & Aging, vol. 12, No. 7, pp. 433-450, (2008).

Centers for Disease Control and Prevention, "Vaccine excipient and media summary", 4 pages, found at www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/excipient-table-2.pdf?utm_content=buffer4538f&utm_medium=social&utm_source=linkedin.com&utm_campaign=buffer, (2015).

Definition of "N(6)-Carboxymethyllysine", printed from Wikipedia, the free encyclopedia on Dec. 8, 2013, 1 page, found at http://en.wikipedia.org/wiki/N(6)-Carboxymethyllysine.

Definition of "Lysine", printed from Wikipedia, the free encyclopedia on Dec. 8, 2013, 1 page, found at http://en.wikipedia.org/wiki/Lysine.

Jarvis, L.M., "Rethinking antibody-drug conjugates", Chemical & Engineering News, vol. 90, issue 25, pp. 12-18, (2012).

Mullin, R., "Cell-free approach to antibody-drug conjugates", Chemical & Engineering News, vol. 91, issue 44, 2 pages, (2013).

Thayer, A.M., "Building antibody-drug conjugates", Chemical & Engineering News, vol. 92, issue 3, pp. 13-21, (2014).

Feige, M.J. et al., "The structural analysis of shark IgNAR antibodies reveals evolutionary principles of immunoglobulins", Proceedings of the National Academy of Sciences, vol. 111, No. 22, pp. 8155-8160, (2014).

Philipot, D. et al.,"$p16^{INK4a}$ and its regulator miR-24 link senescence and chondrocyte terminal differentiation-associated matrix remodeling in osteoarthritis", Arthritis Research & Therapy, vol. 16, No. 1, pp. 1-12, (2014).

International Search Report and Written Opinion dated Mar. 31, 2016 for PCT application No. PCT/US2015/050154.

Zhu, Y. et al., "The achilles' heel of senescent cells: from transcriptome to senolytic drugs", Aging Cell, vol. 14, pp. 644-658, (2015).

DeNardo, S.J. et al., "Development of tumor targeting bioprobes (^{111}in-chimeric L6 monoclonal antibody nanoparticles) for alternating magnetic field cancer therapy", Clinical Cancer Research, vol. 11, 19 supplemental, pp. 7087s-7092s, (2005).

Chen, L. et al., "Cytolysis of human erythrocytes by a covalent antibody-selenium immunoconjugate", Free Radical Biology & Medicine, vol. 19, No. 6, pp. 713-724, (1995).

Yuan, Y. et al., "Advanced glycation end products (AGEs) increase human mesangial foam cell formation by increasing Golgi SCAP glycosylation in vitro", American Journal of Physiology-Renal Physiology, vol. 301.1, pp. F236-F243, (2011).

Liu, H. et al., "Abstract 154: Vaccination using advanced glycation end product of low-density lipoprotein pulsed dendritic cells reduces atherosclerosis in diabetic $apoe^{-/-}$ mice", Arteriosclerosis, Thrombosis, and Vascular Biology, pp. 1-4, (2012).

Mashitah, M.W. et al., "Immunization of AGE-modified albumin inhibits diabetic nephropathy progression in diabetic mice", Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, vol. 8, pp. 347-355, (2015).

Sayej, W.N. et al., "Advanced glycation end products induce obesity and hepatosteatosis in CD-1 wild-type mice", BioMed Research International, vol. 6, No. 39, pp. 1-12, (2016).

Srikanth, V. et al., "Advanced glycation endproducts and their receptor RAGE in alzheimer's disease", Neurobiology of Aging, vol. 32, No. 5, pp. 763-777, (2011).

International Search Report and Written Opinion dated Dec. 2, 2016 for PCT application No. PCT/US2016/039076.

Fu, M-X. et al., "The advanced glycation end product, N-(Carboxymethyl)lysine, is a product of both lipid peroxidation and glycoxidation reactions", The Journal of Biological Chemistry, vol. 271, No. 17, pp. 9982-9986, (1996).

Jorgensen, L. et al., "The relationship between atherosclerosis of the thoracic aorta and renal scarring in an autopsy material", Acta Pathol Microbiol Immunol Scand A., vol. 93, No. 5, pp. 251-255, (1985) Abstract Only.

"Senescent cells drive plaque formation in animal models of atherosclerosis, research shows", Mayo Clinic, pp. 1-2, (2016), found at www.news-medical.net/news/20161027/Senescent-cells-drive-plaque-formation-in-animal-models-of-atherosclerosis-research-shows.aspx.

Arichika, S. et al., "Correlation of retinal arterial wall thickness with atherosclerosis predictors in type 2 diabetes without clinical retinopathy", British Journal of Ophthalmology, vol. 101, pp. 69-74, (2017).

Lin, Z. et al., "Vaccination against AGE-LDL significant attenuates atherosclerosis in diabetic apoe mice", Heart, vol. 97, No. 21, supplement 3, p. A18, (2011) Abstract Only.

Peppa, M. et al., "The role of advanced glycation end products in the development of atherosclerosis", Current Diabetes Reports, vol. 4, pp. 31-36, (2004).

Glenn, J.V. et al., "The role of advanced glycation end products in retinal ageing and disease", Biochimica Et Biophysica Acta, vol. 1790, No. 10. pp. 1109-1116, (2009).

European Search Report dated Feb. 21, 2017 for EP application No. 16198527.0.

U.S. Appl. No. 14/974,095, filed Sep. 22, 2017.

(56) **References Cited**

OTHER PUBLICATIONS

U.S. Appl. No. 14/920,737, filed Oct. 22, 2015.
U.S. Appl. No. 13/876,157, filed Sep. 10, 2015.
U.S. Appl. No. 13/876,157, filed Mar. 30, 2016.
U.S. Appl. No. 13/876,157, filed Oct. 17, 2016.
U.S. Appl. No. 13/876,157, filed Jan. 5, 2017.
U.S. Appl. No. 14/974,095, filed Feb. 13, 2017.
U.S. Appl. No. 14/974,561, filed Jun. 13, 2017.
U.S. Appl. No. 14/974,095, filed Jun. 27, 2017.
U.S. Appl. No. 15/511,731, filed Sep. 15, 2015.
Zhu, L. et al., "Immunization with advanced glycation end products modified low density lipoprotein inhibits atherosclerosis progression in diabetic apoE and Ldlr null mice", Cardiovascular Diabetology, vol. 13, No. 151, pp. 1-12, (2014).
Hashimoto, M. et al., "Elimination of $p19^{ARF}$-expressing cells enhances pulmonary function in mice", JCI Insight, vol. 1, No. 12, pp. 1-15, (2016).
Yan, S.F. et al., "Soluble RAGE: Therapy & biomarker in unraveling the RAGE axis in chronic disease and aging", Biochemical Pharmacology, vol. 79, No. 10, pp. 1379-1386, (2010).
Xue, J. et al., "Advanced glycation end product (AGE) recognition by the receptor for AGEs (RAGE)", Structure, vol. 19, No. 5, pp. 722-732, (2011).
Chang, J. et al., "Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice", Nature Medicine, vol. 22, No. 1, pp. 78-83, (2016).
Geiger, H., "Depleting senescent cells to combat aging", Nature Medicine, vol. 22, No. 1, pp. 23-24, (2016).
Ni, J. et al., "Plasma protein pentosidine and carboxymethyllysine, biomarkers for age-related macular degeneration", Molecular & Cellular Proteomics, vol. 8, No. 8, pp. 1921-1933, (2009).
R&D Systems, a biotechne brand, product specification of "Carboxymethyl Lysine Antibody", found at https://www.rndsystems.com/products/carboxymethyl-lysine-antibody- 318003 mab3247, 1 page, (2015).
Schalkwijk, C.G. et al., "Increased accumulation of the glycoxidation product N^{ϵ}-(carboxymethyl)lysine in hearts of diabetic patients: generation and characterization of a monoclonal anti-CML antibody", Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, vol. 1636, No. 2, pp. 82-89, (2004).
LaPak, K.M. et al., "The molecular balancing act of $p16^{INK4a}$ in cancer and aging", Molecular Cancer Research, vol. 12, No. 2, pp. 167-183, (2013).
Larsen, S.A. et al., "Glucose metabolite glyoxal induces senescence in telomerase-immortalized human mesenchymal stem cells", Chemistry Central Journal, vol. 6, No. 18, pp. 1-13, (2012).
Ahmed, M.U. et al., "N^{ϵ}-(carboxymethyl)lysine, a product of the chemical modification of proteins by methylglyoxal, increases with age in human lens proteins", Biochemical Journal, vol. 324, pp. 565-570, (1997).
Dunn, J.A. et al., "Age-dependent accumulation of N^{ϵ}-(Carboxymethyl)lysine and N^{ϵ}- (Carboxymethyl)hydroxylysine in human skin collagen", Biochemistry, vol. 30, pp. 1205-1210, (1991).
Finco, A.B. et al., "Generation and characterization of monoclonal antibody against advanced glycation end products in chronic kidney disease", Biochemistry and Biophysics Reports, vol. 6, pp. 142-148, (2016).
International Search Report and Written Opinion dated Aug. 10, 2016 for PCT application No. PCT/US2016/034880.
Baker, D.J. et al., "Naturally occurring $p16^{Ink4a}$-positive cells shorten healthy lifespan", Nature, vol. 530, issue 7589, pp. 184-189, (2016).
Raquib, R., "The key to youth via senescent cell removal", Young Investigators Review, pp. 1-4, (2017), found at sbyireview.com/2017/01/23/the-key-to-youth-via-senescent-cell-removal.
Tiner, S., "Mayo clinic research links senescent cells and atherosclerosis progression", Mayo Clinic News Network, pp. 1-3, (2016), found at newsnetwork.mayoclinic.org/discussion/mayo-clinic-research-links-senescent-cells-and-atherosclerosis-progression.
Wiley, C., "Aging Fundamentals: Cellular senescence", Science of Aging Blog at the Buck Institute, pp. 1-4, (2015), found at sage.buckinstitute.org/aging-fundamentals-cellular-senescence.
Thompson, L.V., "Age-related muscle dysfunction", Experimental Gerontology, vol. 44, pp. 106-111, (2009).
Sun, K. et al., "Elevated serum carboxymethyl-Lysine, an advanced glycation end product, predicts severe walking disability in older women: The women's health and aging study I", Journal of Aging Research, vol. 2012, pp. 1-8, (2012).
Kislinger, T. et al., "N^{ϵ}-(Carboxymethyl)Lysine adducts of proteins are ligands for receptor for advanced glycation end products that activate cell signaling pathways and modulate gene expression", The Journal of Biological Chemistry, vol. 274, No. 44, pp. 31740-31749, (1999).
Nakayama, H. et al., "Production and characterization of antibodies to advanced glycation products on proteins", Biochemical and Biophysical Research Communications, vol. 162, No. 2, pp. 740-745, (1989).
Gupta, R.K., "Aluminum compounds as vaccine adjuvants", Advanced Drug Delivery Review, vol. 32, No. 3, pp. 155-172, (1998), Abstract Only.
Tracy, J.M. et al., "Preservatives for poliomyelitis (Salk) vaccine II: Formaldehyde and esters of p-hydroxybenzoic acid", Journal of Pharmaceutical Sciences, vol. 53, Issue 6, pp. 659-663, (1964), Abstract Only.
Koito, W. et al., "Conventional antibody against N^{ϵ}-(Carboxymethyl)Lysine (CML) shows cross-reaction to N^{ϵ}-(Carboxyethyl)Lysine (CEL): Immunochemical quantification of CML with a specific antibody", The Journal of Biochemistry, vol. 135, No. 6, pp. 831-837, (2004).
Product Description of "Anti-Advanced Glycation End Products (AGE), Carboxy-Methyl Lysine (CML) [6C7] Antibody", Kerafast, www.kerafast.com/product/1779/anti-advanced-glycation-end-products-age-carboxy-methyl-lysine-cml-6c7-antibody, printed on Feb. 2, 2017.
Ikeda, K. et al., "N^{ϵ}-(Carboxymethyl)lysine protein adduct is a major immunological epitope in proteins modified with advanced glycation end products of the maillard reaction", Biochemistry, vol. 35, No. 24, pp. 8075-8083, (1996).
Dunn, J.A. et al., "Oxidation of glycated proteins: Age-dependent accumulation of N^{ϵ}-(Carboxymethyl)lysine in lens proteins", Biochemistry, vol. 28, No. 24, pp. 9464-9468, (1989).
Xu, M. et al., "Transplanted senescent cells induce an osteoarthritis-like condition in mice", The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, pp. 1-6, (2016).
Ratliff, M. et al., "In senescence, age-associated B cells secrete TNFα and inhibit survival of B-cell precursors", Aging Cell, vol. 12, pp. 303-311, (2013).
Manestar-Blazic, T. et al., "The dynamic of senescent cells accumulation can explain the age-specific incidence of autoimmune diseases", Medical Hypotheses, vol. 73, pp. 667-669, (2009).
Tchkonia, T. et al., "Fat tissue, aging, and cellular senescence", Aging Cell, vol. 9, pp. 667-684, (2010).
Robbins, P. et al., "Scripps research, Mayo Clinic scientists find new class of drugs that dramatically increases healthy lifespan", The Scripps Research Institute, pp. 1-3, found at www.scripps.edu/news/press/2015/20150309agingcell.html, printed on Mar. 14, 2015.
Dorr, J.R. et al., "Synthetic lethal metabolic targeting of cellular senescence in cancer therapy", Nature, vol. 501, No. 7467, pp. 421-425, (2013).
Xu, M. et al., "Targeting senescent cells enhances adipogenesis and metabolic function in old age", eLife, vol. 4, pp. 1-20, (2015).
Minamino, T. et al., "Endothelial cell senescence in human atherosclerosis: Role of telomere in endothelial dysfunction", Circulation, vol. 105, issue 13, pp. 1541-1544, (2002).
Takino, J-I. et al., "Cancer malignancy is enhanced by glyceraldehyde-derived advanced glycation end-products", Journal of Oncology, vol. 2010, pp. 1-8, (2010).
Laberge, R-M. et al., "Epithelial-mesenchymal transition induced by senescent fibroblasts", Cancer Microenvironment, vol. 5, pp. 39-44, (2012).

(56) **References Cited**

OTHER PUBLICATIONS

Abe, R. et al., "Regulation of human melanoma growth and metastasis by AGE-AGE receptor interactions", Journal of Investigative Dermatology, vol. 122, No. 2, pp. 461-467, (2004).

Porporato, P.E. et al., "A mitochondrial switch promotes tumor metastasis", Cell Reports, vol. 8, pp. 754-766, (2014).

Boquio, A. et al., "Reversible cell cycle inhibition and premature aging features imposed by conditional expression of p161^{ink4a}", Aging Cell, vol. 14, pp. 139-147, (2015).

Nelson, G. et al., "A senescent cell bystander effect: senescence-induced senescence", Aging Cell, vol. 11, pp. 345-349, (2012).

Rayess, H. et al., "Cellular senescence and tumor suppressor gene p16", International Journal of Cancer, vol. 130, No. 8, pp. 1715-1725, (2012).

Greenfieldboyce, N., "Boosting life span by clearing out cellular clutter", NPR.ORG, 4 pages, found at www.npr.org/sections/health-shots/2016/02/03/465354874/boosting-lifespan-by-clearing-out-cellular-clutter, printed on Feb. 4, 2016.

Matus, D.Q. et al., "Invasive cell fate requires G1 cell-cycle arrest and histone deacetylase-mediated changes in gene expression", Developmental Cell, vol. 35, pp. 162-174, (2015).

Stony Brook University, "Targeting invasive cells not dividing cells to halt cancer, study suggests", ScienceDaily, pp. 1-2, found at www.sciencedaily.com/releases/2015/10/151026181610.htm, (2015).

Liu, D. et al., "Senescent human fibroblasts increase the early growth of xenograft tumors via matrix metalloproteinase secretion", Cancer Research, vol. 67, No. 7, pp. 3117-3126, (2007).

Hoke, Z. "Belgian researchers discover way to block cancer metastasis", VOZ News, pp. 1-3, found at www.voanews.com/a/belgian-researchers-discover-way-to-block-cancer-metastasis/2453790.html, (2014).

Di, G-H. et al., "IL-6 secreted from senescent mesenchymal stem cells promotes proliferation and migration of breast cancer cells", PloS one, vol. 9, No. 11, pp. 1-15, (2014).

Huang, L-W. et al., "P16^{ink4a} overexpression predicts lymph node metastasis in cervical carcinomas", Journal of Clinical Pathology, vol. 65, pp. 117-121, (2012).

Romagosa, C. et al., "P16^{ink4a} overexpression in cancer: a tumor suppressor gene associated with senescence and high-grade tumors", Oncogene, vol. 30, pp. 2087-2097, (2011).

Terman, A. et al., "Mitochondrial turnover and aging of long-lived postmitotic cells: The mitochondrial-lysosomal axis theory of aging", Antioxidants & Redox Signaling, vol. 12, No. 4, pp. 503-535, (2010).

Ralph, A. et al., "P16 and HPV discordance in metastatic carcinoma of cervical lymph nodes of unknown primary", Clinical Case Reports, vol. 3, No. 10, pp. 817-818, (2015).

Hipkiss, A.R. "Aging, proteotoxicity, mitochondria, glycation, NAD+ and carnosine: possible inter-relationships and resolution of the oxygen paradox", Frontiers in Aging Neuroscience, vol. 2, article 10, pp. 1-6, (2010).

Bakala, H. et al., "Changes in rat liver mitochondria with aging Ion protease-like activity and N$^{\varepsilon}$-carboxymethyllysine accumulation in the matrix", European Journal of Biochemistry, vol. 270, No. 10, pp. 2295-2302, (2003).

Leslie, M. "Suicide of aging cells prolongs life span in mice", Sciencemag.org, pp. 1-4, found at www.sciencemag.org/news/2016/02/suicide-aging-cells-prolongs-life-span-mice, (2016).

Eto, H. et al., "Selective imaging of malignant ascites in a mouse model of peritoneal metastasis using in vivo dynamic nuclear polarization-magnetic resonance imaging", Analytical Chemistry, vol. 88, pp. 2021-2027, (2016).

May Jr. K.F. et al., "Anti-human CTLA-4 monoclonal antibody promotes T-cell expansion and immunity in a hu-PBL-SCID model: a new method for preclinical screening of costimulatory monoclonal antibodies", Blood, vol. 105, pp. 1114-1120, (2005).

Schmitt, C.A. "Cellular senescence and cancer treatment", Biochimica et Biophysica Acta—Reviews on Cancer, vol. 1775, No. 1, pp. 5-20, (2007).

Gordon, R.R. et al., "Cellular senescence and cancer chemotherapy resistance", Drug Resistance Updates, vol. 15, No. 1-2, pp. 123-131, (2012).

Eyman, D. et al., "CCL5 secreted by senescent aged fibroblasts induces proliferation of prostate epithelial cells and expression of genes that modulate angiogenesis", Journal of Cellular Physiology, vol. 220, No. 2, pp. 376-381, (2009).

Nguyen, D.X. et al., "Metastasis: from dissemination to organ-specific colonization", Nature Reviews Cancer, vol. 9, No. 4, pp. 274-284, (2009).

Smit, M.A. et al., "Deregulating EMT and senescence: Double impact by a single twist", Cancer Cell, pp. 5-7, (2008).

Degenhardt, T.P. et al., "Chemical modification of proteins by methylglyoxal", Cellular and Molecular Biology (Noisy-le-Grand, France), vol. 44, No. 7, pp. 1139-1145, (1998) Abstract Only.

Gao, S.H. et al., "Monoclonal antibody humanness score and its applications", BMC Biotechnology, vol. 13, No. 1, pp. 1-12, (2013).

ClinicalTrials.gov, "A study evaluating the safety of ABT-263 in combination with etoposide/cisplatin in subjects with cancer", ClinicalTrials.gov, 4 pages, found at https://clinicaltrials.govict2/show/NCT00878449?term=A+study+evaluating+the+safety+of+ABT-263+in+combination+with+etoposide%2Fcisplatin+in+subjects+with+cancer&rank=1, printed on Aug. 4, 2016.

Keating, D.J. "Mitochondrial dysfunction, oxidative stress, regulation of exocytosis and their relevance to neurodegenerative diseases", vol. 104, No. 2, pp. 298-305, (2008). Abstract Only.

Sas, K. et al., "Mitochondria, metabolic disturbances, oxidative stress and the kynurenine system, with focus on neurodegenerative disorders", Journal of the neurological sciences, vol. 257, No. 1, pp. 221-239, (2007). Abstract Only.

Ott, M. et al., "Mitochondria, oxidative stress and cell death", Apoptosis, vol. 12, No. 5, pp. 913-922, (2007). Abstract Only.

Trushina, E. et al., "Oxidative stress and mitochondrial dysfunction in neurodegenerative diseases", Neuroscience, vol. 145, No. 4, pp. 1233-1248, (2007). Abstract Only.

Moreira, P.I. et al., "Lipoic acid and N-acetyl cysteine decrease mitochondrial-related oxidative stress in Alzheimer disease patient fibroblasts", Journal of Alzheimer's Disease, vol. 12, No. 2, pp. 195-206, (2007). Abstract Only.

Yel, L. et al., "Thimerosal induces neuronal cell apoptosis by causing cytochrome c and apoptosis-inducing factor release from mitochondria", International Journal of Molecular Medicine, vol. 16, No. 6, pp. 971-977, (2005). Abstract Only.

Humphrey, M.L. et al., "Mitochondrial mediated thimerosal-induced apoptosis in a human neuroblastoma cell line (SK-N-SH)", Neurotoxicology, vol. 26, No. 3, pp. 407-416, (2005). Abstract Only.

Makani, S. et al., "Biochemical and molecular basis of thimerosal-induced apoptosis in T cells: a major role of mitochondrial pathway", Genes and Immunity, vol. 3, No. 5, pp. 270-278, (2002). Abstract Only.

Freitag, H. et al., "Inhibition of malate transport and activation of phosphate transport in mitochondria by ethylmercurithiosalicylate", FEBS Letters, vol. 117, No. 1, pp. 149-151, (1980). Citation Only.

Freitag, H. et al., "Ethylmercurithiosalicylate—a new reagent for the study of phosphate transport in mitochondria", FEBS Letters, vol. 114, No. 2, pp. 295-298, (1980). Citation Only.

Windham, G.C. et al., "Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco bay area", Environmental Health Perspectives, pp. 1438-1444, (2006). Citation Only.

Ooe, H. et al., "Induction of reactive oxygen species by bisphenol A and abrogation of bisphenol A-induced cell injury by DJ-1", Toxicological Sciences, vol. 88, No. 1, pp. 114-126, (2005). Abstract Only.

Hanzel, C.E. et al., "Thallium induces hydrogen peroxide generation by impairing mitochondrial function", Toxicology and Applied Pharmacology, vol. 216, No. 3, pp. 485-492, (2006). Abstract Only.

Murugavel, P. et al., "Cadmium induced mitochondrial injury and apoptosis in vero cells: protective effect of diallyl tetrasufide from garlic", The International Journal of Biochemistry & Cell Biology, vol. 39, No. 1, pp. 161-170, (2007). Abstract Only.

(56) **References Cited**

OTHER PUBLICATIONS

Lasfer, M. et al., "Cadmium induces mitochondria-dependent apoptosis of normal human hepatocytes", Cell Biology and Toxicology, vol. 24, No. 1, pp. 55-62, (2008). Abstract Only.
Gash, D.M. et al., "Trichloroethylene: Parkinsonism and complex 1 mitochondrial neurotoxicity", Annals of neurology, vol. 63, No. 2, pp. 184-192, (2008). Abstract Only.
Banerjee, N. et al., "Arsenic-induced mitochondrial instability leading to programmed cell death in the exposed individuals", Toxicology, vol. 246, No. 2, pp. 101-111, (2008). Abstract Only.
Partridge, M.A. et al., "Arsenic induced mitochondrial DNA damage and altered mitochondrial oxidative function: Implication for genotoxic mechanisms in mammalian cells", Cancer Research, vol. 67, No. 11, pp. 5239-5247, (2007). Abstract Only.
Santra, A. et al., "Arsenic induces apoptosis in mouse liver is mitochondria dependent and is abrogated by N-acetylcysteine", Toxicology and Applied Pharmacology, vol. 220, No. 2, pp. 146-155, (2007). Abstract Only.
Bouchard, H. et al., "Antibody-drug conjugates—A new wave of cancer drugs", Bioorganic & Medicinal Chemistry Letters, vol. 24, pp. 5357-5363, (2014).
Yang, H.M. et al., "Doxorubicin conjugated with a monoclonal antibody directed to a human melanoma-associated proteoglycan suppresses the growth of established tumor xenografts in nude mice", Proceeding of the National Academy of Science, vol. 85, pp. 1189-1193, (1988).
Childs, B.G. et al., "Senescent intimal foam cells are deleterious at all stages of atherosclerosis", Science, vol. 354, No. 6311, pp. 472-477, (2016).
Loaiza, N. et al., "Cellular senescence and tumor promotion: Is aging the key?", Biochimica et Biophysica Acta, vol. 1865, pp. 155-167, (2016).
Rodier, F. et al., "Four faces of cellular senescence", The Journal of Cell Biology, vol. 192, No. 4, pp. 547-556, (2011).
Shay, J.W. et al., "Hallmarks of senescence in carcinogenesis and cancer therapy", Oncogene, vol. 23, pp. 2919-2933, (2004).
Davalos, A.R. et al., "Senescent cells as a source of inflammatory factors for tumor progression", Cancer Metastasis Reviews, vol. 29, pp. 273-283, (2010).
Roninson, I.B., "Tumor cell senescence in cancer treatment", Cancer Research, vol. 63, pp. 2705-2715, (2003).
International Search Report and Written Opinion dated May 17, 2017 for PCT application No. PCT/US2017/018185.
Kobayashi, S. et al., "Overproduction of N(epsilon)-(carboxymethyl) lysine-induced neovascularization in cultured choroidal explant of aged rat", Biological & Pharmaceutical Bulletin, vol. 30, No. 1, pp. 133-138, (2007).
Foster, D. et al., "AGE metabolites: A biomarker linked to cancer disparity?" Cancer Epidemiology, Biomarkers and Prevention, vol. 23, No. 10, pp. 2186-2191, (2014).
Mir, A.R. et al., "Structural changed in histone H2A by methylglyoxal generate highly immunogenic amorphous aggregates with implications in auto-immune response in cancer", Glycobiology, vol. 26, No. 2, pp. 129-141, (2016).
Ko, S-Y. et al., "Cell migration is regulated by AGE-RAGE interaction in human oral cancer cells in vitro", PLOS One, vol. 9, No. 10, pp. 1-9, (2014).
Chen, H. et al., "Advanced glycation end products increase carbohydrate responsive element binding protein expression and promote cancer cell proliferation", Molecular and Cellular Endocrinology, vol. 395, No. 1-2, pp. 69-78, (2014).
Mercado-Pimentel, M.E. et al., "The S100P/RAGE signaling pathway regulates expression of microRNA-21 in colon cancer cells", FEBS Letters, vol. 589, No. 18, pp. 2388-2393, (2015).
Product description, "Carboxymethyl Lysine Antibody", R&D Systems, a biotechne brand, catalog No. MAB3247, 1 page, found at https://resources.rndsystems.com/pdfs/datasheets/mab3247.pdf, (2015).
Bhat, R. et al., "Astrocyte senescence as a component of Alzheimer's Disease", PLOS One, vol. 7, No. 9, pp. 1-10, (2012).
Flanary, B.E. et al., "Evidence that aging and amyloid promote microglial cell senescence", Rejuvenation Research, vol. 10, No. 1, pp. 61-74, (2007).
Takeda, A. et al., "Advanced glycation end products co-localize with astrocytes and microglial cells in Alzheimer's disease brain", Acta Neuropathologica, vol. 95, pp. 555-558, (1998).
Chinta, S.J. et al., "Environmental stress, ageing and glial cell senescence: a novel mechanistic link to Parkinson's disease?", Journal of Internal Medicine, vol. 273, pp. 429-436, (2013).
Mori, M., "The Parkinsonian Brain: Cellular senescence and neurodegeneration", SAGE, found at sage.buckinstitute.org/the-parkinsonian-brain-cellular-senescence-and-neurodegeneration, (2015).
Das, M.M. et al., "Astrocytes show reduced support of motor neurons with aging that is accelerated in a rodent model of ALS", Neurobiology of Aging, vol. 36, pp. 1130-1139, (2015).
Luessi, F. et al., "Neurodegeneration in multiple sclerosis: novel treatment strategies", Expert Rev. Neurother., vol. 9, pp. 1061-1077, (2012).
Wright, W.E., "Myoblast senescence in Muscular Dystrophy", Exp Cell Research, vol. 157, pp. 343-354, (1985).
King, O.D., et al., "The tip of the iceberg: RNA-binding proteins with prion-like domains in neurodegenerative disease", Brain Research, vol. 1462, pp. 61-80, (2012).
Dobson, D.M., "The structural basis of protein folding and its links with human disease", Philosophical Transactions of the Royal Society of London B: Biological Sciences, vol. 356, No. 1406, pp. 133-145, (2001).
Kato, S. et al., "Advanced glycation endproduct-modified superoxide dismutase-1 (SOD1)-positive inclusions are common to familial amyotrophic lateral sclerosis patients with SID1 gene mutations and transgenic mice expressing human SOD1 with a G85R mutation", Acta Neuropathologica, vol. 100, pp. 490-505, (2000).
U.S. Appl. No. 12/994,421, filed Jun. 14, 2012.
U.S. Appl. No. 12/951,768, filed Jul. 2, 2012.
U.S. Appl. No. 12/951,768, filed Mar. 30, 2012.
U.S. Appl. No. 12/994,421, filed Jul. 20, 2012.
U.S. Appl. No. 12/994,421, filed Sep. 10, 2012.
U.S. Appl. No. 12/951,768, filed Nov. 5, 2012.
U.S. Appl. No. 12/994,421, filed Feb. 26, 2013.
U.S. Appl. No. 12/951,768, filed Mar. 21, 2013.
U.S. Appl. No. 12/951,768, filed Mar. 27, 2013.
U.S. Appl. No. 12/994,421, filed May 21, 2013.
U.S. Appl. No. 12/994,421, filed Jul. 18, 2013.
U.S. Appl. No. 12/951,768, filed Jul. 29, 2013.
U.S. Appl. No. 12/951,768, filed Nov. 15, 2013.
U.S. Appl. No. 12/951,768, filed Dec. 20, 2013.
U.S. Appl. No. 13/332,976, filed Sep. 3, 2014.
U.S. Appl. No. 14/247,081, filed Sep. 9, 2014.
U.S. Appl. No. 13/332,976, filed Nov. 18, 2014.
U.S. Appl. No. 12/994,421, filed Nov. 18, 2014.
U.S. Appl. No. 14/247,081, filed Jan. 13, 2015.
U.S. Appl. No. 14/247,081, filed Feb. 2, 2015.
U.S. Appl. No. 12/994,421, filed Mar. 13, 2015.
U.S. Appl. No. 13/332,976, filed Mar. 13, 2015.
U.S. Appl. No. 12/994,421, filed Mar. 27, 2015.
U.S. Appl. No. 13/332,976, filed Apr. 1, 2015.
U.S. Appl. No. 13/332,976, filed Apr. 23, 2015.
U.S. Appl. No. 13/332,976, filed May 1, 2015.
U.S. Appl. No. 14/247,081, filed May 6, 2015.
U.S. Appl. No. 13/332,976, filed Jun. 11, 2015.
U.S. Appl. No. 14/247,081, filed Jul. 10, 2015.
U.S. Appl. No. 14/247,081, filed Jul. 21, 2015.
U.S. Appl. No. 12/994,421, filed Sep. 2, 2015.
U.S. Appl. No. 12/994,421, filed Jan. 19, 2016.
U.S. Appl. No. 14/974,095, filed Sep. 22, 2016.
U.S. Appl. No. 14/932,200, filed Nov. 4, 2015.
U.S. Appl. No. 14/974,561, filed Dec. 18, 2015.
U.S. Appl. No. 14/974,095, filed Dec. 18, 2015.
Forbes, J.M. et al., "Below the radar: Advanced glycation end products that detour "around the side"", Clinical Biochemist Reviews, vol. 26, pp. 123-134, (2005).
Paul, W.E., "Fundamental immunology, third edition", Raven Press New York, chapter 9, pp. 292-295, (1993).

(56) **References Cited**

OTHER PUBLICATIONS

Rudikoff, S. et al., "Single amino acid substitution altering antigen-binding specificity", Proceedings of the National Academy of Science USA, vol. 79, pp. 1979-1983. (1982).

Wu, H. et al., "Humanization of a murine monoclonal antibody by simultaneous optimization of framework and CDR residues", Journal of rylolecular Biology, vol. 294, pp. 151-162, (1999).

Golay, J. et al., "Mechanism of action of therapeutic monoclonal antibodies: Promises and pitfalls of in vitro and in vivo assays", Archives of Biochemistry and Biophysics, vol. 526, pp. 146-153, (2012).

Tang, S-S. et al., "Reaction of aortic lysyl oxidase with β-Aminopropionitrile", The Journal of Biological Chemistry, vol. 258, No. 7, pp. 4331-4338, (1983).

Saito, H. et al., "Regulation of a novel gene encoding a lysyl oxidase-related protein in cellular adhesion and senescence", The Journal of Biological Chemistry, vol, 272, No. 13, pp. 8157-8160, (1997).

Choi, Y-G. et al., "N^{ϵ}-carboxymethyl modification of lysine residues in pathogenic prion isoforms", Molecular Neurobiology, vol. 53, pp. 3102-3112, (2016).

Wendel, U. et al., "A novel monoclonal antibody targeting carboxymehyllysine, an advanced glycation end product in atherosclerosis and pancreatic cancer", PLoS One, vol. 13, No. 2, pp. 1-22, (2018).

Hsia, T-C. et al., "Carboxymethyllysine, an advanced glycation end-product, promotes the invasion and migration of lung cancer A549 cells", Clinical Medicine Research, vol. 6, No. 5, pp. 149-156, (2017).

Nowotny, K., et al., "Advanced glycation end products and oxidative stress in type 2 diabetes mellitus", Biomolecules, vol. 5, pp. 194-222, (2015).

Yun, M.H. et al., "Recurrent turnover of senescent cells during regeneration of a complex structure", eLIFE, elifesciences.org, pp. 1-16, (2015).

Barja, G., "Aging in vertebrates, and the effect of caloric restriction: a mitochondrial free radical production-DNA damage mechanism?", Biological Reviews, vol. 79, No. 2, pp. 235-251, (2004). Abstract Only.

Pamplona, R. et al., "Aging increases nepsilon-(carboxymethyl)lysine and caloric restriction decreases nepsilon-(carboxyethyl)lysine and nepsilon-(malondialdehyde)lysine in rat heart mitochondrial proteins", Free Radical Research, vol. 36, No. 1, pp. 47-54, (2002). Abstract Only.

Yun, M.H., "Cellular senescence in regeneration", The Node, pp. 1-8, found at http://thenode.biologists.com/cellular-senescence-in-regeneration/research/, Jun. 28, 2015.

Kasper, M. et al., "Age-related changes in cells and tissues due to advanced glycation end products (AGEs)", Archives of Gerontology and Geriatrics, vol. 32, issue 3, pp. 233-243, (2001). Abstract Only.

Wang, Z. et al., "Advanced glycation end-product Nϵ-carboxymethyl-Lysine accelerates progression of atherosclerotic calcification in diabetes", Atherosclerosis, vol. 221, issues 2, pp. 387-396, (2012). Abstract Only.

Draber, P. et al., "Stability of monoclonal IgM antibodies freeze-dried in the presence of trehalose", Journal of Immunological Methods, vol. 181, issue 1, pp. 37-43, (1995).

Kesari, S. et al., "Pritumumab binding to glioma cells induces ADCC and inhibits tumor growth", Journal of Clinical Oncology, vol. 35, No. 15 Supplemental, e14004-e14004, (2017). Abstract Only.

Babic, I. et al., "Pritumumab, the first therapeutic antibody for glioma patients", Human Antibodies, vol. 26, No. 2, pp. 95-101, (2017). Abstract Only.

Riva, P. et al., "Treatment of intracranial human glioblastoma by direct intratumoral administration of ^{131}I-labelled anti-tenascin monoclonal antibody BC-2", International Journal of Cancer, vol. 51, No. 1, pp. 7-13, (1992). Abstract Only.

Ruster, M. et al., "Detection of elevated N^{ϵ}-carboxymethyllysine levels in muscular tissue and in serum of patients with fibromyalgia". Scandinavian Journal of Rheumatology, vol. 34, issue 6, pp. 460-463, (2005). Abstract Only.

Niwa, H. et al., "Accelerated formation of N^{ϵ}-(carboxymethyl) lysine, an advanced glcation end product, by glyoxal and 3-deoxyglucosone in cultured rat sensory neurons", Biochemical and Biophysical Research Communications, vol. 248, issue 1, p, 93-97, (1998), Abstract Only.

Daly, C. et al., "Monocyte chernoattractant protein-1 (CCL2) in inflammatory disease and adaptive immunity: Therapeutic opportunities, and controversies", Microcirculation, vol, 10, pp. 247-257, (2003).

Lee, S.T. et al., "Decreased number and function of endothelial progenitor cells in patients with migraine", Neurology, vol. 70, No. 17, 1510-1517, (2008). Abstract Only.

Brown, J.N. et al., "Class effect of erythropoietin therapy on hemoglobin A_{1C} in a patient with diabetes mellitus and chronic kidney disease not undergoing hemodialysis", Pharmacotherapy, The Journal of Human Pharmacology and Drug Therapy, vol. 29, No. 4. pp. 468-472, (2009). Abstract Only.

Liu, J. et al., "Accelerated senescence of renal tubular epithelial cells is associated with disease progression of patients with immunoglobulin A (IgA) nephropathy", Translational Research, vol. 169, issue 6, pp. 454-463, (2012), Abstract Only.

Khaw, K-T. et al., "Association of hemoglobin A_{1C} with cardiovascular disease and mortality in adults: The European prospective investigation into cancer in Norfolk", Annals of Internal Medicine, vol. 141, pp. 413-420, (2004).

Kohnert, K.D. et al., "Destruction of pancreatic beta cells in rats by complete Freund's adjuvant combined with non-diabetogenic doses of streptozotocin", Diabetes Research, vol. 5, No. 1, pp. 1-11, (1987). Abstract Only.

Staud, R., "Fibromyalgia pain: do we know the source?", Current Opinion in Rheumatology, vol. 16, issue 2, pp, 157-163, (2004). Abstract Only.

Fleurence, J. et al., "Targeting and killing glioblastoma with monoclonal antibody to O-acetyl O-acetyl GD2 ganglioside", Oncotarget, vol. 7, No. 27, pp. 41172-41185. (2016).

Velarde. M.C. et al., "Senescent cells and their secretory phenotype as targets for cancer therapy", Interdisciplinary Topics in Gerontology, vol. 38, pp. 17-27, (2013).

Wang, Z. et al., "CML/RAGE signal induces caici,ication cascade in diabetes", Diabetology & Metabolic Syndrome. vol. 8, No. 33, pp. 1-12, (2016).

Freise, A.C. et al., "In vivo imaging with antibodies and engineered fragments", Molecular Immunology, vol. 67, issue 2, pp. 142-162, (2015).

Pavlides, S. et al., "The reverse Warburg effect: Aerobic glycolysis in cancer associated fibroblasts and the tumor stroma", Cell Cycle, vol. 8, No. 23, pp. 3984-4001, (2009).

Dunn, G.P. et al., "Principles of immunology and its nuances in the central nervous system", Neuro-Oncology, vol. 17, pp. vii3-vii8, (2015).

Rettig, M.P. et al., "Evaluation of biochemical changes during in vivo erythrocyte senescence in the dog", Blood, vol. 93, No. 1, pp. 376-384, (1999).

Baralbar, M.A. et al., "Proteomic quantification and identification of carbonylated proteins upon oxidative stress and during cellular aging", Journal of Proteomics, vol. 92, pp. 63-70, (2013). Abstract Only.

Chaudhuri, J. et al., "A Caenorhabditis elegans model elucidates a conserved role for TRPA1-Nrf signaling in reactive α-dicarbonyl detoxification", Current Biology, vol. 26, pp. 3014-3025, (2016).

Saleh, T. et al., "Reversibility of chemotherapy-induced senescence is independent of autophagy and a potential model for tumor dormancy and cancer recurrence", bioRxiv, pp. 1-29, 5 figures. (2017).

Hubert, P. et al., "Antibody-dependent cell cytotoxicity in monoclonal antibody-mediated tumor immunotherapy", OncoImmunology, vol. 1, issue 1, pp. 103-105, (2012).

(56) **References Cited**

OTHER PUBLICATIONS

Ouchi, R. et al., "Senescence from glioma stem cell differentiation promotes tumor growth", Biochemical and Biophysical Research Communications, vol. 470, No. 2, pp. 275-281, (2016).

Evans, A., et al., "Differentiating benign from malignant solid breast masses: value of shear wave elastography according to lesion stiffness combined with greyscale ultrasound according to BI-RADS classification", British Journal of Cancer, vol. 107, pp. 224-229, (2012).

Walen, K.H., "Normal human cell conversion to 3-D cancer-like growth: Genome damage, endopolyploidy, senescence escape, and cell polarity change/loss", Journal of Cancer Therapy, vol. 2, pp. 181-189, (2011).

Virella, G. et al., "Development of capture assays for different modifications of human low-density lipoprotein", Clinical and Diagnostic Laboratory Immunology, vol. 12, No. 1, pp. 68-75, (2005).

Moghaddam, A.E. et al., "Reactive carbonyls are a major Th2-inducing damage-associated molecular pattern generated by oxidative stress", The Journal of Immunology, vol. 187, pp. 1626-1633, (2011).

Kuilman, T. et al., "The essence of senescence", Genes & Development, vol. 24, pp. 2463-2479, (2010).

James, E.L. et al., "Senescent human fibroblasts show increased glycolysis and redox homeostasis with extracellular metabolomes that overlap with those of irreparable DNA damage, aging, and disease", Journal of Proteome Research, vol. 14, pp. 1854-1871, (2015).

Hein, G. et al., "Are advanced glycation end-product-modified proteins of pathogenetic importance in fibromyalgia?" Rheumatology, vol. 41, pp. 1163-1167, (2002).

Beausejour, C.M. et al., "Reversal of human cellular senescence: roles of the p53 and p16 pathways", The EMBO Journal, vol. 22, No. 16, pp. 4212-4222, (2003).

Simpson, R.J., "Aging, persistent viral infections, and immunosenescence: Can exercise "make space"?", Exercise and Sport Sciences Reviews, vol. 39, No. 1, pp. 23-33, (2011).

Gudkov, A., "Andrei Gudkov taped an expanded presentation of the slides he presented at 2017 Biology of Aging conference at Scripps, Florida, Jan. 22-27", Everon Biosciences, found at everonbio.com/Andrei-gudkov-taped-an-expanded-presentation-of-the-slides-he-presented-at-2017-biology-of-aging-conference-at-scripps-florida-22-27-january, 2 pages, Mar. 21, 2017. Abstract Only.

Radoi, V. et al., "Advanced glycation end products in diabetes mellitus: Mechanism of action and focused treatment", Proceedings of the Romanian Academy, Series B, vol. 1, pp. 9-19, (2012).

Sieben, C.J. et al., "Two-step senescence-focused cancer therapies", Trends in Cell Biology, pp. 1-15, (2018).

Gaens, K.H.J. et al., "N^{ε}-(carboxymethyl)lysine-receptor for advanced glycation end product axis is a key modulator of obesity-induced dysregulation of adipokine expression and insulin resistance", Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 34, issue 6, pp. 1199-1208, pp. s1-s9, (2014).

Semba, R.D. et al., "Relationship of an advanced glycation end product, plasma carboxymethyl-lysine, with slow walking speed in older adults: the inCHIANTI study", European Journal of Applied Physiology, vol. 108, No. 1, pp. 191-195, (2010).

Wu, J. et al., "Sonoporation, anti-cancer drug and antibody delivery using ultrasound", Ultrasonics, vol. 44, supplement, pp. e21-e25, (2006). Abstract Only.

Meerwaldt, R. et al., "Skin autofluorescence is a strong predictor of cardiac mortality in diabetes", Diabetes Care, vol. 30, No. 1, pp. 107-112. (2007).

Nagai, R. et al., "Antibody-based detection of advanced glycation end-products: promises vs. limitations", Glycoconjugate Journal, vol. 33, No. 4, pp. 545-552, (2016).

Schmidt, A.M. et al., "The biology of the receptor for advanced glycation end products and its ligands", Biochimica et Biophysica Acta, vol. 1498, pp. 99-111, (2000).

Berens, M.E. et al., """. . . those left behind." Biology and oncology of invasive glioma cells", Neoplasia, vol. 1, No. 3, pp. 208-219, (1999).

Hansen, K. et al., "Microneedle enabled intradermal delivery of biologics", 3M Drug Delivery Systems, 1 page, printed on Jul. 25, 2018.

SELECTIVE REMOVAL OF AGE-MODIFIED CELLS FOR TREATMENT OF ATHEROSCLEROSIS

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to provisional application No. 61/386,932 entitled "SELECTIVE REMOVAL OF AGE-MODIFIED CELLS FOR TREATMENT OF ATHEROSCLEROSIS" filed 27 Sep. 2010, the entire contents of which are hereby incorporated by reference, except where inconsistent with the present application.

BACKGROUND

Aging cells undergo several modifications associated with diseased conditions. Hyperglycemia, caused by diabetes mellitus (DM), and oxidative stress promote post-translational modifications of membrane proteins of cells by advanced glycation end-products (AGE). Lindsey J B, et al., "Receptor For Advanced Glycation End-Products (RAGE) and soluble RAGE (sRAGE): Cardiovascular Implications," *Diabetes Vascular Disease Research*, Vol. 6(1), 7-14, (2009) at p. 8. AGE arise from a nonenzymatic reaction of sugars with protein side-chains in aging cells and is involved in the pathogenesis of several age-related disease processes, including adverse complications of diabetes. Ando K, et al., "Membrane Proteins of Human Erythrocytes Are Modified by Advanced Glycation End Products During Aging in the Circulation," *Biochemical and Biophysical Research Communications*, Vol. 258, 123-27 (1999) at p. 123.

AGE-modified erythrocytes have less flexibility than non-modified erythrocytes, and have been implicated in the pathogenesis of atherosclerosis, while the absence of AGE-modified erythrocytes has been correlated with reduced atherosclerosis. Jandeleit-Dahm K, et al., "The AGE/RAGE Axis in Diabetes-Accelerated Atherosclerosis," *Clinical and Experimental Pharmacology and Physiology*, Vol. 35, 329-334 (2008) at 330. Localization of AGEs in atherosclerotic lesions of the aorta in non-diabetic patients has been reported in intima cells, endothelial cells, smooth muscle cells, macrophages and foam cells. Sakata N. et al., "Immunohistochemical Localization of Different Epitopes of Advanced Glycation End Products in Human Atherosclerotic Lesions," *Atherosclerosis,* 141, 61-75 (1998) at p. 71. The damage caused by AGE-modified cells may also lead to nephropathy, retinopathy, neuropathy, heart disease, stroke, and peripheral vascular disease. Karachalias N. et al., "Accumulation of Fructosyl-Lysine and Advanced Glycation End Products in the Kidney, Retina and Peripheral Nerve of Streptozotocin-Induced Diabetic Rats." *Biochemical Society Transactions,* 31, 1423-25 (2003) at 1423.

SUMMARY

In a first aspect, the present invention is a method of treating atherosclerosis comprising removing AGE-modified cells from a patient.

In a second aspect, the present invention is a method of removing AGE-modified erythrocytes from blood, comprising damaging or destroying an AGE-modified erythrocyte with ultrasound.

In a third aspect, the present invention is a method of removing AGE-modified cells, comprising binding the AGE-modified cells with an anti-AGE monoclonal antibody.

In a fourth aspect, the present invention is a method of removing AGE-modified cells from atherosclerotic lesions, comprising binding the AGE-modified cells with an anti-AGE monoclonal antibody.

DEFINITIONS

The following definitions are included to provide a clear and consistent understanding of the specification and claims.

The term "advanced glycation end-products" refers to the aggregate of glycated proteins on the cell membrane that are formed as the result of the reaction of sugars with protein side chains, and are also referred to as AGE-modified proteins and AGE-modified cells.

DETAILED DESCRIPTION

The present invention makes use of the discovery that enhanced clearance of AGE-modified cells, such as erythrocytes, is beneficial in reducing cardiovascular disease, especially when present as a complication of diabetes, or the pre-diabetic condition referred to as "Syndrome-X". Elevated blood glucose concentrations lead to modifications of protein side chains in cells, including circulating erythrocytes and other cell types. Non-enzymatic glycation of membrane proteins results in the formation of AGE-modified cells, which cause reduced cell deformability that is associated with the formation of atherosclerotic lesions.

The technique for removing AGE-modified erythrocytes from a patient is selected for its ability to detect and selectively remove or destroy AGE-modified cells while avoiding removal or destruction of cells that are not AGE-modified. For example, AGE-modified erythrocytes may be detected due to their increased stiffness and reduced deformability by ultrasound. In an example, ultrasound treatment may be applied at driving frequencies ranging from 1.0 Mhz to 5.0 Mhz, preferably from 3.0 Mhz to 4.0 Mhz. Time of exposure may range from three to sixty minutes daily for up to 20 days.

Additionally, anti-AGE monoclonal antibodies may be used for their ability to selectively bind AGE-modified cells. Anti-AGE monoclonal antibodies bind to AGE-modified cells, such as AGE-modified erythrocytes, to selectively remove the AGE-modified cells from a patient. The blood from the patient may be passed through extracorporeal circulation and AGE-modified erythrocytes are then bound by anti-AGE monoclonal antibodies attached to a solid substrate via their Fc region.

Further, anti-AGE monoclonal antibodies covalently conjugated to a fluorescent marker may be used to label AGE-modified erythrocytes that are then removed from the patient's blood via cell sorting. An anti-AGE monoclonal antibody is injected into the patient to label AGE-modified erythrocytes and, subsequently, the patient's blood is connected to a cell sorter via extracorporeal circulation tubing system. AGE-modified erythrocytes bound to a fluorescent anti-AGE monoclonal antibody are sorted from normal erythrocytes and other blood cell types.

Anti-AGE monoclonal antibodies can be conjugated to an agent that causes the destruction of AGE-modified cells. Such agent can be, but is not limited to a toxin, a cytotoxic agent, magnetic nanoparticles, and magnetic spin-vortex discs.

Moreover, AGE-modified cell types localized in atherosclerotic lesions of the aorta in non-diabetic patients, such as intima cells, endothelial cells, smooth muscle cells, macrophages, and foam cells, may be selectively removed by

using anti-AGE monoclonal antibodies conjugated to an agent that causes the destruction of AGE-modified cells. Such agent can be, but is not limited to a toxin, a cytotoxic agent, magnetic nanoparticles, and magnetic spin-vortex discs.

A toxin, such as pore-forming toxins (PFT) (Aroian R. et al., "Pore-Forming Toxins and Cellular Non-Immune Defenses (CNIDs)," *Current Opinion in Microbiology,* 10:57-61 (2007)), conjugated to an anti-AGE monoclonal antibody may be injected into a patient to selectively target and remove AGE-modified cells. The anti-AGE monoclonal antibody recognizes and binds to AGE-modified erythrocytes or AGE-modified cells present in atherosclerotic lesions. Then, the toxin causes pore formation at the cell surface and subsequent cell removal through osmotic lysis (Id. at p. 58).

Magnetic nanoparticles conjugated to anti-AGE monoclonal antibodies may be injected into a patient to target and remove AGE-modified erythrocytes or AGE-modified cells present in atherosclerotic lesions. The magnetic nanoparticles can be heated by applying a magnetic field in order to selectively remove the AGE-modified erythrocytes or AGE-modified cells present in atherosclerotic lesions.

As an alternative, magnetic spin-vortex discs, which are magnetized only when a magnetic field is applied to avoid self-aggregation that can block blood vessels, begin to spin when a magnetic field is applied, causing membrane disruption of target cells. Magnetic spin-vortex discs, conjugated to anti-AGE monoclonal antibodies specifically target AGE-modified cell types, without removing other cells.

EXAMPLES

Example 1 (Prophetic) Ultrasound Removal of AGE-Modified Erythrocytes in ZDF (Zucker Diabetic Fatty) Rats

In this example ZDF rats, a type II diabetic rat model demonstrating obesity, insulin resistance, hyperinsulinemia, hyperglycemia, hypertriglyceridemia, hypercholesterolemia, nephropathy, impaired wound healing, mild hypertension, and neuropathy, are exposed to ultrasound to determine (1) the background level of glycated hemoglobin A1c in this strain; (2) whether exposure to ultrasound at clinical imaging levels, is tolerable by assessing clinical observation on the animals; (3) whether there is an effect on the level of glycated hemoglobin A1c due to exposure to ultrasound. The level of glycated hemoglobin A1c is used as a marker for removal of AGE-modified erythrocytes.

Ten ZDF rats, approximately eight weeks old at receipt, supplied by Charles River Laboratories (Wilmington, Mass.) are randomly assigned in two groups, labeled I and II. The animals are weighed prior to ultrasound exposure. The rats are shaved dorsally and ultrasound gel is applied by pressing and rubbing the applicator across the dorsal aspect of the rat, from thorax from tail. While one technician holds the animal, another uses the applicator. The ultrasound machine is set at 3.3 Mhz and the applicator is pressed against the dorsal aspect of the animal and moved slowly from thorax to tail for the appropriate time of exposure. Rats in group I are exposed to five minutes of ultrasound at 3.3 Mhz/day for ten days and rats in group II are exposed to ten minutes of ultrasound at 3.3 Mhz/day for ten days. Following exposure the animal is wiped off to remove ultrasound gel and placed back in its cage. The animals remain under observation for four hours within four hours from exposure for any clinical evaluation. Blood samples are taken from each animal via retro-orbital bleeding prior to exposure to ultrasound, then at day five, and after the last exposure, at day ten. To analyze the blood samples a (GhbA1c) ELISA kit (Cusabio Biotech Co., Ltd, Japan) is used. All data documenting experimental details and study procedures are recorded and analyzed to assess effect on the levels of glycated hemoglobin A1c.

Example 2 (Prophetic) Removal of AGE-Modified Erythrocytes by Monoclonal Antibodies

In this example, anti-AGE monoclonal antibody 6D12 (Ando K. et al., supra), or anti-AGE humanized monoclonal antibody is conjugated to a toxin, such as pore-forming toxins or PTFs (Aroian R. et al., Pore-Forming Toxins and Cellular Non-Immune Defenses (CNIDs), *Current Opinion in Microbiology,* 10:57-61 (2007)), magnetic nanoparticles, magnetic spin-vortex discs (Dobson J., "A Twist on Tumour Targeting," *Nature Materials,"* 9, 95-96 (2010)), or a cytotoxic agent, such as selenocystamine, and IP injected in ZDF rats to selectively bind and remove AGE-modified erythrocytes.

ZDF rats are IP injected in the volume of 200 μl for the initial loading dose of 10 mg/kg of the anti-AGE-monoclonal antibody or with 200 μl PBS 1× control. Each rat receives an IP injection per week for a total of six weeks. The animals are weighed weekly and are observed daily for any clinical evaluation. Blood samples are taken from each animal via retro-orbital bleeding every week. The level of glycated hemoglobin A1c is used as a marker for removal of AGE-modified erythrocytes. All data documenting experimental details and study procedures are recorded and analyzed to assess effect on the levels of glycated hemoglobin A1c.

Example 3 (Prophetic) Removal of AGE-Modified Erythrocytes by Panning Selection

In this example, AGE-modified erythrocytes are isolated from a patient by panning selection, using an anti-AGE monoclonal antibody. Extracorporeal blood purification is utilized to remove AGE-modified cells from a patient.

The patient's blood is passed through an extracorporeal tubing system containing a sorbent agent, i.e. an anti-AGE monoclonal antibody to selectively remove AGE-modified erythrocytes from the blood. Anti-AGE monoclonal antibodies attached to a solid substrate through their Fc region, bind AGE-modified erythrocytes and remove them from the patient's blood. The blood is recirculated through extracorporeal circulation to remove most AGE-modified erythrocytes and the duration of the procedure is performed following standards known in the art for removing other corpuscolated elements from the blood, e.g. platelets. Gutensohn K. et al., "Extracorporeal Plateletpheresis Induces the Interaction of Activated Platelets with White Blood Cells," *Vox Sanguinis*, Vol. 78(2), 101-05 (2000). At the end of the procedure, the patient's intracorporeal circulation is restored.

Alternatively, an anti-AGE monoclonal antibody conjugated to a marker, e.g. a fluorescent marker, is injected into a patient. The patient's blood is passed through an extracorporeal tubing system connected to a cell sorter. AGE-modified erythrocytes bound to anti-AGE monoclonal antibodies are sorted by selecting the fluorescent erythrocytes and therefore removed from the patient's blood. At the end of the procedure, the patient's intracorporeal circulation is restored.

Example 4 (Prophetic) Removal of AGE-Modified Erythrocytes by Pore-Forming Toxins (PFTs)

In this example, AGE-modified erythrocytes are targeted by anti-AGE monoclonal antibodies conjugated to a pore-forming toxin. Pore-forming toxins cause osmotic lysis in erythrocytes. Pore-forming toxins can be conjugated to monoclonal antibody to specifically target a particular cell type. See for example, U.S. Pat. No. 5,817,771, "Cell Targeted Lytic Pore-Forming Agents."

Anti-AGE monoclonal antibodies conjugated to a pore-forming toxin are injected in a patient. The anti-AGE monoclonal antibodies selectively bind and cause the lysis of AGE-modified erythrocytes via the conjugated pore-forming toxin.

Example 5 (Prophetic) Removal of AGE-Modified Cells in Atherosclerotic Lesions by Pore-Forming Toxins (PFTs)

In this example, AGE-modified cells in atherosclerotic lesions are targeted by anti-AGE monoclonal antibody 6D12 (Ando K. et al., supra), or anti-AGE humanized monoclonal antibody conjugated to a toxin, such as pore-forming toxins or PTFs (Aroian R. et al., supra). Pore-forming toxins cause osmotic lysis in AGE-modified cells. Pore-forming toxins can be conjugated to monoclonal antibody to specifically target a particular cell type. See for example, U.S. Pat. No. 5,817,771, "Cell Targeted Lytic Pore-Forming Agents."

Anti-AGE monoclonal antibodies conjugated to a pore-forming toxin are injected in a patient. The anti-AGE monoclonal antibodies selectively bind and cause the lysis of AGE-modified cells in atherosclerotic lesions, such as intima cells, endothelial cells, smooth muscle cells, macrophages, and foam cells, via the conjugated pore-forming toxin.

REFERENCES

1. Lindsey J B, et al., "Receptor for Advanced Glycation End-Products (RAGE) and soluble RAGE (sRAGE): Cardiovascular Implications," *Diabetes Vascular Disease Research*, Vol. 6(1), 7-14, (2009).
2. Ando K, et al., "Membrane Proteins of Human Erythrocytes Are Modified by Advanced Glycation End Products During Aging in the Circulation," *Biochemical and Biophysical Research Communications*, Vol. 258, 123-27 (1999).
3. Jandeleit-Dahm K, et al., "The AGE/RAGE Axis in Diabetes-Accelerated Atherosclerosis," *Clinical and Experimental Pharmacology and Physiology*, Vol. 35, 329-334 (2008).
4. Sakata N. et al., "Immunohistochemical Localization of Different Epitopes of Advanced Glycation End Products in Human Atherosclerotic Lesions," *Atherosclerosis,* 141, 61-75 (1998).
5. Karachalias N. et al., "Accumulation of Fructosyl-Lysine and Advanced Glycation End Products in the Kidney, Retina and Peripheral Nerve of Streptozotocin-Induced Diabetic Rats." *Biochemical Society Transactions,* 31, 1423-25 (2003).
6. Aroian R. et al., Pore-Forming Toxins and Cellular Non-Immune Defenses (CNIDs), *Current Opinion in Microbiology,* 10:57-61 (2007).
7. Dobson J., "A Twist on Tumour Targeting," *Nature Materials,"* 9, 95-96 (2010).

What is claimed is:

1. A method of cleansing blood, comprising removing AGE-modified erythrocytes from blood,

wherein the AGE-modified erythrocytes are removed by binding with an anti-AGE monoclonal antibody.

2. The method of claim **1**, wherein the anti-AGE monoclonal antibody is conjugated to an agent selected from the group consisting of a toxin or a cytotoxic agent, magnetic nanoparticles, and magnetic spin-vortex discs.

3. The method of claim **1**, wherein the AGE-modified erythrocytes are removed ex vivo.

4. The method of claim **3**, wherein the AGE-modified erythrocytes are removed by cell sorting.

5. The method of claim **3**, wherein the AGE-modified erythrocytes are removed by panning selection.

6. The method of claim **1**, wherein the anti-AGE monoclonal antibody is attached to a solid substrate.

7. The method of claim **1**, wherein the anti-AGE monoclonal antibody is covalently conjugated to a marker.

8. The method of claim **7**, wherein the marker comprises a fluorescent marker.

9. The method of claim **1**, wherein the anti-AGE monoclonal antibody is conjugated to an agent selected from the group consisting of a toxin or a cytotoxic agent, magnetic nanoparticles, and magnetic spin-vortex discs,

the AGE-modified erythrocytes are removed ex vivo, and the removing comprises cell sorting or panning selection.

10. A method of treating atherosclerosis, comprising removing AGE-modified erythrocytes from blood,

wherein the AGE-modified erythrocytes are removed by binding with an anti-AGE monoclonal antibody.

11. The method of claim **10**, wherein the anti-AGE monoclonal antibody is conjugated to an agent selected from the group consisting of a toxin or a cytotoxic agent, magnetic nanoparticles, and magnetic spin-vortex discs.

12. The method of claim **10**, wherein the AGE-modified erythrocytes are removed ex vivo.

13. The method of claim **12**, wherein the AGE-modified erythrocytes are removed by cell sorting.

14. The method of claim **12**, wherein the AGE-modified erythrocytes are removed by panning selection.

15. The method of claim **10**, herein the anti-AGE monoclonal antibody is attached to a solid substrate.

16. The method of claim **10**, wherein the anti-AGE monoclonal antibody is covalently conjugated to a marker.

17. The method of claim **16**, wherein the marker comprises a fluorescent marker.

18. The method of claim **10**, wherein the anti-AGE monoclonal antibody is conjugated to an agent selected from the group consisting of a toxin or a cytotoxic agent, magnetic nanoparticles, and magnetic spin-vortex discs,

the AGE-modified erythrocytes are removed ex vivo, and the removing comprises cell sorting or panning selection.

19. A method of treating atherosclerosis, comprising removing AGE-modified enythrocytes from a patient,

wherein the AGE-modified erythrocytes are removed by binding with an anti-AGE monoclonal antibody.

20. The method of claim **19**, wherein the patient is a human.

21. The method of claim **19**, wherein the patient has Syndrome X or diabetes.

22. The method of claim **19**, wherein the anti-AGE monoclonal antibody is conjugated to an agent selected from the group consisting of a toxin or a cytotoxic agent, magnetic nanoparticles, and magnetic spin-vortex discs.

23. The method of claim **19**, wherein the antibodies are humanized.

24. The method of claim **22**, wherein the anti-AGE monoclonal antibody is conjugated to a cytotoxic agent, and the cytotoxic agent comprises selenocystamine.

25. The method of claim **19**, further comprising testing the patient for removal of AGE-modified erythrocytes.

26. The method of claim **25**, wherein the testing comprises measuring the levels of glycated hemoglobin A1c.

27. The method of claim **19**, wherein the patient is a human,

the antibodies are humanized, and

the anti-AGE monoclonal antibody is conjugated to an agent selected from the group consisting of a toxin or a cytotoxic agent, magnetic nanoparticles, and magnetic spin-vortex discs.

28. The method of claim **27**, further comprising testing the patient for removal of AGE-modified erythrocytes.

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